A Dissertation on

Study of Clinical Significance of Unrecognized Renal Dysfunction in Patients with Acute Stroke

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In partial fulfillment of the Regulations for the Award of the Degree of

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CERTIFICATE BY THE INSTITUTION

This is to certify that **Dr. P.KALAVATHI,** Post - Graduate Student (MAY 2015 TO APRIL 2018) in the Department of General Medicine STANLEY MEDICAL COLLEGE, Chennai- 600 001, has done this dissertation on "**Study of Clinical Significance of Unrecognized Renal Dysfunction in Patients with Acute Stroke"** under my guidance and supervision in partial fulfillment of the regulations laid down by the Tamilnadu Dr. M. G. R. Medical University, Chennai, for M.D. (General Medicine), Degree Examination to be held in April 2018.

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DECLARATION

I, **Dr. P. KALAVATHI,** declare that I carried out this work on "**Study of Clinical Significance of Unrecognized Renal Dysfunction in Patients with Acute Stroke"** in the Medical wards of Government Stanley Hospital. I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award, degree, or diploma to any other university, board either in India or abroad.

This is submitted to The Tamilnadu DR. M. G. R. Medical University, Chennai in partial fulfillment of the rules and regulation for the M. D. Degree examination in General Medicine.

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Certificate

This is to certify that this dissertation work titled "**Study of Clinical Significance of Unrecognized Renal Dysfunction in Patients with Acute Stroke,** of the candidate **Dr. KALAVATHI P** with registration number - 201511055 for the award of **M.D**. in the branch of **GENERAL MEDICINE**. I personally verified the http://www.urkund.com/en/ website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows 3 percentage of plagiarism in the dissertation.

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11

CONTENTS

ABSTRACT

Introduction: Unrecognized renal insufficiency, defined as an estimated glomerular filtration rate <60 mL/min/1.73 m2 in the presence of normal serum creatinine levels, is a common comorbid condition among patients with various cardiovascular conditions. The current study was aimed to evaluate the prevalence and clinical significance of unrecognized renal dysfunction in patients admitted with acute stroke.

Methods: This cross sectional study consisted of patients with acute stroke admitted in medical ward at Stanley medical college. Estimated glomerular filtration is estimated using MDRD and CKD – EPI formula. Study group is divided into three groups (normal renal function, unrecognized and recognized renal dysfunction) as per eGFR. The two primary outcomes such as severe disability at hospital discharge and in-hospital mortality are compared in each group.

Results: Of the 100 patients with stroke included in the study, 62% had normal renal function, 31% had recognized renal insufficiency, and 7% had unrecognized renal insufficiency. Mortality rates are higher in patients with recognized and unrecognized renal insufficiency compared with patients with normal renal function (29%, %, and 28.5% and 9.6%) respectively, P <

0.04053). Similarly, severe disability rates at discharge are also higher in patients with recognized and unrecognized renal insufficiency compared with patients with normal renal function (72.27%, 80 %, and 32.14%) respectively.

Conclusion: Unrecognized renal insufficiency is common among patients with acute stroke and is associated with adverse short-term outcomes.

INTRODUCTION

Stroke or cerebrovascular accident is defined as abrupt onset of neurological disorder such as sudden decrease or loss of consciousness, voluntary movement or sensation caused by occlusion of blood vessel or rupture. Renal insufficiency is a strong predictor of adverse out-comes in patients with various cardiovascular disorders including stroke. Despite its clinical significance, renal insufficiency is frequently unrecognized. Although the renal function has been assessed routinely using serum creatinine, it is an unreliable proxy influenced by various factors including age, sex, race, and lean body weight. Patients with serum creatinine levels slightly more than the upper limit or even within the normal range may have renal dysfunction, which may often be clinically significant. The term unrecognized renal insufficiency is defined as an estimated glomerular filtration rate <60 mL/min/1.73 m2 in the presence of serum creatinine ≤ 1.2 mg/ dl. The group of patients having unrecognized renal insufficiency signify a high-risk group with greater mortality rate compared to patients with normal renal function. Hence, renal function in stroke patients should be assessed by glomerular filtration rate instead of serum creatinine.

Review of Literature

2.1 Brain Anatomy

The most metabolically active organ in our body is brain. Although it represents merely 2% of the body mass, it serves numerous vital functions and requires 15 to 20% of cardiac output at rest. Cerebral hemispheres form the greater part of the brain and are supplied by 3 paired major arteries named anterior, middle and posterior cerebral arteries. Anterior circulation is carried by anterior and middle cerebral artery. Middle cerebral artery is the dominant arterial source to the brain. It supplies the lateral portions of frontal, parietal, temporal lobes, anterior portion of temporal lobe, Globus pallidus, Putamen and Internal capsule. Posterior circulation is carried by Posterior cerebral artery which supplies thalamus, brainstem, posterior and medial parts of temporal and occipital lobes.

2.2 Cerebrovascular Accident

Stroke or cerebrovascular accident is defined as abrupt onset of neurological disorder such as sudden decrease or loss of consciousness, voluntary movement or sensation caused by breach or occlusion (as by a clot) of a blood vessel of the brain—also known as brain attack, apoplexy, cerebral accident or cerebrovascular accident. Stroke is the third major cause of morbidity and

mortality in india [40] after myocardial infarction. It is one of the important causes of adult disability. Direct causes are

1) Cerebral thrombosis

2) Cerebral aneurysm rupture

3) Severe rise in blood pressure causing hemorrhage or ischemia [25] and

4) Cerebral embolism

Stroke may be hemorrhagic or ischemic. Almost 85% of all strokes are ischemic. But hemorrhagic stroke is responsible for 30% of all stroke deaths. Ischemic stroke may turn into hemorrhagic transformation after reperfusion especially in patients treated with thrombolysis or endovascular intervention [4, 13].

Latest studies found that reduced GFR is associated with both hemorrhagic as well as ischemic stroke. Hence, renal dysfunction is an independent risk factor (table 1) for mortality outcome of stroke as well as new cardiovascular events [3, 9, and 2].

Table 1 Risk factors for stroke

All age groups	Younger age
Elderly, age >55 years	Protein C, S deficiencies
Hypertension, Diabetes, CKD	Antithrombin III deficiency
Smoking, Alochol intake	Antiphospholipid syndrome
Arrhythmias	Factor V Leiden mutation
Dilated cardiomyopathy	Sickle cell anemia
Family H/O stroke	Hyperhomocysteinaemia
Vasculitis	Arterial dissection
Use of cocaine or amphetamines	Thrombotic thrombocytopenic purpura
Oral contraceptives intake	Syphilis, HIV

2.2.1 Cicinnati Prehospital stroke scale

In prehospital phase this scale is used to detect stroke early. It can be remembered by acronym "FAST" – Facial asymmetry, Arm drift, Speech abnormality and Time of onset. Common stroke signs and symptoms are abrupt onset of limb weakness in the form of monoparesis, hemiparesis or quadriparesis, hemisensory deficits, visual defects, sudden decrease in the level of consciousness, diplopia, Dysarthria, Facial droop, ataxia, vertigo and nystagmus [6].

Table 2 Differences between Hemorrhagic, Thrombotic and Embolic strokes

Feature	Hemorrhagic	Thrombotic	Embolic
Time of onset	During activity	In sleep	Any time
Progression	Over minutes	Over hours	Within seconds
TIAs	Absent	Present	Present
Vomiting	Recurrent	-	-
Headache	Prominent	-	-
Early resolution within minutes or days	Unusual	Variable	Possible
Meningeal irritation	+/-	-	-
Carotid bruit	-	Highly supportive	Possible
Valvular heart disease & Atrial fibrillation	-	Unusual	Highly supportive
CT brain	Hemorrhage	Pale infarct	Pale infarct, Hemorrhagic infarct in some cases

2.2.2 Ischemic stroke

It is characterized by sudden cessation of blood circulation to a particular area of brain, leading to loss of neurological function corresponding to that area. It is caused by embolic or thrombotic occlusion of a cerebral artery. An ischaemic stroke classically presents with rapid onset neurological deficit, which is determined by the area of brain supplied by the involved artery. The signs and symptoms usually evolve over hours, and may deteriorate or recover, depending on the destiny of the ischaemic penumbra. Types of ischemic stroke are transient

ischemic attacks, completed stroke, lacunar infarcts and watershed infarcts. Multifocal small infarcts or ischemia may produce slowly progressive neurological disorders – multi infarct dementia and subcortical arteriosclerotic encephalopathy (Binswanger's disease). The brain has no glucose storage and also more sensitive to hypoxia. Therefore, any critical reduction of cerebral blood flow for more than 2 -3 minutes will rapidly instigate a cellular level ischemic cascade ultimately leading to cell death [10,39].

Table 3 Fate of brain tissue and cerebral blood flow

Events	Cerebral blood flow (%)
Normal	>50
Oligaemia-reduced cerebral blood flow but retained neuronal activity	21-50
Ischemic penumbra-Loss of electrical activity but viable tissue	11-20
Irreversible neuronal death	6-10

2.2.3 Transient ischemic attacks

It is a transitory episode of neurological deficit, not lasting more than 24 hours due to ischemia of a particular region of the brain or retinal ischemia with normal neuroimaging without any evidence of acute infarction. So it is not possible to diagnose TIA without diagnostic imaging [8]. TIA occurs due to a platelet thrombus getting detached from an atherosclerotic plaque to produce

short lasting blockade at a distal branch. Then embolus gets broken down and disappear resulting in restoration of perfusion with reversal of neurological dysfunction.

Factors associated with high risk of recurrence of stroke within three months

1) Age more than 60 years

2) Symptom duration more than 10 minutes

3) Weakness

4) Speech impairment

5) Diabetes mellitus

Causes of TIAs:

1) Large artery atherosclerosis – Carotid stenosis, Vertebrobasilar disease, Aortic atherosclerosis.

2) Cardio aortic embolism – Atrial fibrillation, Valvular heart disease, Left ventricle thrombus.

3) Intracranial small vessel diseases from long standing hypertension, intracranial atherosclerosis.

4) Others – Hypercoagulable states, Arterial dissection

2.2.4 Stroke in evolution

In few patients focal neurological deficits may worsen stepwise over few hours or days. It occurs due to gradual occlusion of major blood vessel by a thrombus. It may also occur in a rapidly growing tumor and subdural hematoma [7].

2.2.5 Lacunar infarction

They are small deep infarcts usually less than 15mm. Occurs secondary to diseases of small perforating branches of brain. Lacunar infarction is usually associated with hypertension, Diabetes, Smoking or micro embolism from heart or carotid arteries. Causes of lacunar stroke are lipohyalinosis, micro atheroma, fibrinoid necrosis due to hypertension or vasculitis, hyaline arteriosclerosis, amyloid angiopathy and microemboli. There are five classic syndromes in lacunar stroke are as follows; a) pure motor stroke, b) pure sensory stroke, c) mixed sensorimotor stroke, d) ataxic hemiparesis and e) dysarthria clumsy hand syndrome.

2.2.6 Watershed infarct

Ischemia that is localized to the vulnerable border zones between the tissues supplied by anterior, middle and posterior cerebral arteries is called watershed infarct. It contributes about 10% of all ischemic strokes. They are particularly susceptible to infarction from profound hypo perfusion. They are localized to two primary regions of brain, cortical watersheds and internal watersheds.

2.2.7 Ischemic Penumbra

The area surrounding an ischemic area of the brain is named as Penumbra. Penumbra is defined as ischemic tissue potentially destined for infarction but still it is reversible if treated properly and hence, the target for any acute therapies. Reducing blood pressure in acute ischemic stroke can damage penumbra irreversibly. But there is no accurate blood pressure target has been defined yet. AHA guidelines recommend not reducing BP unless it exceeds 220/120 mmHg [11].

2.2.8 Types of Hemorrhagic strokes

There are four types of hemorrhagic strokes, including 1) Primary intracerebral hemorrhage, 2) Primary intraventricular hemorrhage, 3) Subarachnoid hemorrhage and 4) Intracerebral hemorrhage. The common sites of hypertensive bleeding are Putamen, Thalamus, Frontal, Parietal lobes, Pons and Cerebellum.

2.2.9 Subarachnoid hemorrhage

Subarachnoid hemorrhage accounts for 10% of all strokes. Common causes are rupture of aneurysm of circle of willis, AV malformations, Trauma, extension of intracerebral bleed, Mycotic aneurysm, Bleeding diathesis and anticoagulant treatment. Characteristic feature is abrupt onset headache with or without vomiting. Headache may be associated with neck stiffness, seizures, loss of consciousness or focal neurological deficits. Rebleeding, hydrocephalus,

hyponatremia, seizures, vasospasm are the common complications of SAH. A study found that even trivial changes in creatinine clearance are associated with considerable worst outcomes in patients with aneurysmal SAH.

2.2.10 Cerebral venous sinus thrombosis

Generally, the cerebral venous sinus thrombosis is the cause 1 -2% of strokes in young adults. Superior sagittal sinus is commonly involved.

2. 2.11 Stroke syndromes

A) Anterior cerebral artery syndrome

Contralateral weakness and sensory loss commonly occur in Lower Limbs. Aphasia, Urinary incontinence, Loss of social inhibition and may have memory deficits.

B) Middle cerebral artery syndrome

Contralateral weakness and sensory loss more commonly occur in face and upper extremities. Homonymous hemianopia, spatial disorganization, Wernicke's aphasia if dominant hemisphere is involved and unilateral neglect

C) Vertebral basilar artery occlusion

1. Headache, dizziness, ataxia

2. Hemiplegia or tetraplegia

3. Cranial nerve palsies

4. Locked in syndrome

5. Loss of consciousness

D) Posterior cerebral artery occlusion

1. Contralateral sensory loss
2. Thalamic pain syndrome – intolerable burning pain and sensory perseveration
3. Memory deficits
4. Homonymous hemianopia
5. Visual agnosia
6. Cortical blindness

E) Differential Diagnosis of stroke

1. Metabolic or Toxic encephalopathy
2. Post ictal Todd's palsy
3. Hemiplegic migraine
4. Hypertensive encephalopathy
5. Conversion disorders
6. Encephalitis, Brain abscess
7. Head injury
8. Structural intracranial lesions
9. Relapsing multiple sclerosis

Table 4 Risk assessment for occurrence of stroke – ABCD2 score*

Predictor	Points
Age > 60 years	1
Blood pressure > 140/90 mmHg	1
Clinical features (maximum 2) Unilateral weakness (2) Speech difficulty without weakness (1)	2
Duration (maximum 2) > 60 mins (2) 10 to 59 mins (1) < 10 mins (0)	2
Diabetes	1
Maximum total score	7

* High risk of early stoke if ABCD2 score more than 3 points.

F) Investigations

Complete blood count may reveal few rare causes for stroke such as polycythemia, leukemia, thrombocytopenia and thrombocytosis. Basic biochemistry investigations like blood sugar, Renal function test, Serum electrolytes to rule metabolic causes of stroke. They also provide evidence for concurrent illness – Diabetes, renal dysfunction and dyselectrolytemia. Serum creatinine helps to calculate EGFR which is more significant to find out renal dysfunction especially unrecognized renal dysfunction. ECG is must to find out

arrhythmias and coronary artery disease. In some patients hemorrhagic stroke may occur due to brain secondary from lung malignancy. Hence, chest x ray should be the part of the routine investigation. It also gives clues about the cardiac size [41].

Young patients need some special investigations such as

- Anti-nuclear antibody screening
- Serological test for syphilis
- Anticardiolipin antibodies
- Protein C, S
- Antithrombin III

CT brain: Non-contrast CT brain remains the mainstay of imaging because it is the fast, relatively inexpensive and readily available investigation in the setting of an acute stroke. However, its main limitation is less sensitivity to find out ischemic stroke in the acute setting. CT brain should be taken immediately to rule out hemorrhage, tumor and subdural hematoma. Large infarcts with edema can be visualized during the first few hours of stroke [41]. The key aims of CT brain in acute setting are 1) rule out intracranial haemorrhage, which would prevent thrombolysis 2) look for early features of infarction 3.exclude other intracranial lesions that may mimic a stroke, such as tumour.

Fig. 1 Acute infarct: images of CT brain

Non contrast CT brain (fig 1) demonstrates acute massive infarct and sulcal effacement including the left anterior and middle cerebral artery territories. Occasionally, earliest sign of acute infarct visible as hyperdense fragment of a vessel, demonstrating direct visualisation of the intravascular embolus / thrombus [41, 42]. Though this could be detected in any vessel, it is most often witnessed in the middle cerebral artery known as hyperdense middle cerebral artery sign. Hyperdense MCA sign is seen within 60 to 90 minutes of the ischemic event. It is the 'golden hour' of thrombolysis to save the patient. This sign is approximately 100% sensitivity, however only 30% specificity.

Fig. 3 Acute Dense MCA sign images of CT brain

Fig. 4 CT brain of acute parenchymal hemorrhage - Plain CT brain shows hyperdense lesion with mass effect in left frontal area.

Fig. 5 CT brain of subarachnoid hemorrhage: High density subarachnoid blood seen in basal cisterns, sylvian fissures and within the fourth ventricle.

Diffusion weighted MRI of brain: It is the most sensitive and specific for ischemic stroke [42].

CT or MR angiography: It is necessary if either intra- arterial fibrinolysis or mechanical thrombectomy [41] has been planned and also to rule out aneurysm.

Carotid Doppler: 4 Vessel Carotid Doppler is a safe, more economic, not much time-consuming and establishing the extra cranial carotid artery causes of cerebrovascular accident [43].

2.2.12 Stroke Prevention

Prevention plays a vital role in preventing mortality and morbidity associated with stroke. It has been assessed that 50% of stroke are preventable by life style modifications and controlling risk factors that are modifiable [14].

A) Control of blood pressure and blood sugar:

Hypertension is the most significant modifiable risk factor for stroke. It adds to 50 to 60% of all strokes (atheroma of main vessels, friability of small cerebral vessels, atrial fibrillation, and left ventricular dysfunction). There is direct relationship between blood pressure and stroke incidence in both normotensive as well as hypertensive group. Fall of 5-6 mm Hg diastolic blood pressure has been associated with a 42% relative risk reduction of first stroke event [15]. Literatures demonstrate that diabetes is also a major risk factor for first ischemic stroke [16, 17]. Furthermore, the role of tight blood sugar control in reducing the risk of stroke event is still unclear [18]. Patients with diabetes have poor recovery, more severe disability score and greater mortality. Rate of recurrent stroke is more in patients having diabetes mellitus when compared to nondiabetic stroke patients [19, 20].

B) Cessation of smoking and alcohol intake

Various types of strokes such as ischemic, hemorrhagic stroke and subarachnoid hemorrhage are strongly associated with smoking. Kurth *et al.*, 2003, reported the risk of hemorrhagic stroke in male as well as female smokers [21, 22]. These studies showed an increased risk of total hemorrhagic stroke, and SAH in females smoking ≥15 cigarettes per day and males smoking ≥20 cigarettes per day. Chronic alcohol consumption more than 60 g / day is associated with

increased risk of developing stroke through various mechanisms [25]. Alcohol induces hypertension, cardiac arrhythmias, enhanced platelet activation and aggregation [23] and cerebral vasospasm [24]. Ethanol itself is a direct neurotoxin.

C) Regular exercise and weight control

Exercise activity, irrespective of weight loss, gives several health benefits exclusively for overweight and obese individuals which in turn prevent many cardiovascular conditions. Weight loss is possible by both exercise and calorie restriction. Combination of exercise and calorie restriction is superior because exercise improves insulin resistance [44].

D) Increasing public awareness about early warning signs of CVA

Stroke is frequently preceded by warning symptoms such as headache, limb weakness, giddiness, face drooping, visual disturbance and difficulty in speech that usually lasts less than five minutes, and does not injure the brain. This typically occurs within seven days of major stroke [45]. Hence, patients who are at high risk of stroke should be educated for early warning signs of stroke.

2.2.13 Management of CVA

Successful care of acute stroke patients relies on “Stroke Chain of Survival”.

1. Detection of onset of stroke signs and symptoms early

2. Dispatch through activation of emergency medical services and prompt response
3. Delivery of patient to a pre- notified hospital with appropriate prehospital care
4. Immediate emergency department triage
5. Data compilation including CT brain
6. Decision regarding potential therapies
7. Drug therapy
8. Timely transfer to stroke unit

A) General measures

Treatment of comorbid conditions like reduction of fever, correct hypo or hypertension, correct hypo or hyperglycemia and management of myocardial ischemia and arrhythmias.

BP control: Urgent reduction of BP is necessary only when the blood pressure is more than 220/120 mmHg or mean arterial pressure is more than 130mmHg [4]. And also if the patient has pulmonary edema, renal failure, acute myocardial infarction, etc. In patients undergoing thrombolytic therapy antihypertensives are needed if BP more than 185/110mmHg.

B) Anti edema measures

Anti-edema measures is used in large infarct with significant edema. Commonly 20% Mannitol 0.25mg/Kg has been used along with furosemide.

C) Thrombolytic therapy

Ischemic stroke therapies include fibrinolytic therapy, antiplatelet agents and mechanical thrombectomy. Intravenous recombinant tissue plasminogen activator is useful if initiated within 3-4 hours. Contraindications to thrombolysis are hemorrhagic CVA, bleeding diathesis, BP more than 185/110 mmHg, major neurosurgery or head injury within 3 months, H/O intracranial hemorrhage or AV malformation or active internal bleeding. Intra-arterial thrombolysis via carotid artery can be given within 6 hours. If patients present with more than 6 hours thrombolysis is not useful.

D) Anticogulants

Anticoagulants are recommended only in mild ischemic events in the presence of stroke in evolution.

1) Atrial fibrillation
2) Prosthetic valves

Previous myocardial infarction with akinetic ventricles

Cerebral venous sinus thrombosis

E) Management of Subarachnoid hemorrhage

Antihypertensives if systolic BP is more than 140mmHg. Beta blockers are the drug of choice if there are no contraindications. Nimodipine is useful as it reduces cerebral vasospasm .Nitrates should be avoided because they elevate intracranial pressure. Hyperventilation should be avoided because it may potentiate vasospasm and ischemia. Head end should be elevated at 30 degree to improve venous drainage. Endovascular clipping or coiling of aneurysm is indicated to prevent rebleeding [23].

F) Management of hemorrhagic CVA

If intracerebral hemorrhage volume less than 10 ml or patients present with minimal neurological deficits, consider non-surgical conservative management. Surgery is required if cerebellar hemorrhage more than 3 cm, intracerebral hemorrhage with structural vascular lesion and in young patients with lobar hemorrhage. Surgical approaches are craniotomy and clot evacuation under direct visual guidance, stereotactic aspiration with thrombolytic agents and endoscopic evacuation.

2.2.14 Secondary complications in CVA

Stroke patients are susceptible to various complications such as deep vein thrombosis, bed sores, complex regional pain syndrome, decreased flexibility

and aspiration pneumonitis [46]. Aspiration pneumonitis is the most common cause of death in stroke.

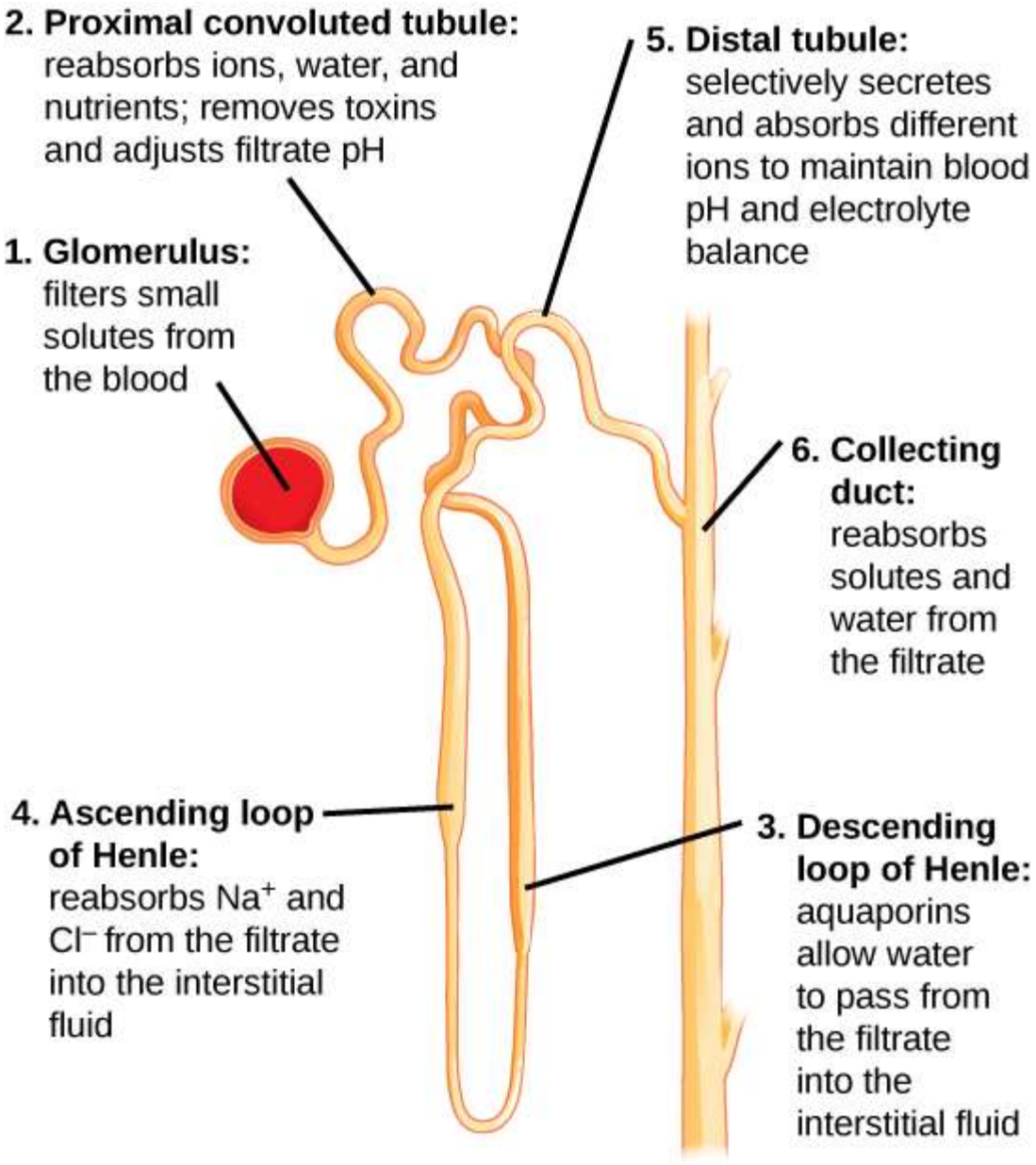
2.2.15 Recovery

Most survivors of a stroke have residual disability. Rehabilitation in the initial six months period should focus to maximize patient's physical activity and to be continued regularly.

2.3 Renal System

2.3.1 Anatomy of the Kidneys

The two kidneys are retroperitoneal organ located in the posterior abdominal wall. Each kidney weighs about 150 grams. Renal vessels, lymphatics, nerve and ureter pass through the hilum present in medial side of each kidney. The kidney is enclosed in a thick fibrous capsule that protects inner delicate structures. The kidney is divided into outer cortex and the inner medulla. The inner medulla is divided into 8 to 10 renal pyramids. The renal pyramids originate at the junction between cortex and medulla and end in papilla, which project into the renal pelvis. Functional unit of the kidney is smallest micro anatomical structure named as nephron. Nephron is divided into proximal and distal convoluted tubule connected by loop of henle. Each segment of the nephron consists of functionally and structurally characteristic cells. [27]



2.3.2 Functions of the Kidneys

The kidneys are the principal organs to excrete waste products that are produced by metabolism or digestion of ingested food. These products include creatinine from creatine phosphate in muscle, urea from amino acids metabolism, uric acid from nucleic acids, bilirubin from hemoglobin and heme containing enzymes,

and metabolites of many hormones. The kidneys also excrete most toxins, drugs and food additives. The most important function of kidneys is to maintain internal balance of, particularly water and electrolytes such as sodium, potassium, chloride, calcium, phosphorus and magnesium [33]. The kidneys also have got endocrine function. It synthesizes erythropoietin which is needed for red blood production and 1, 25-dihydroxycholecalciferol (calcitriol) necessary for bone formation. Most important homeostatic functions are

1) Excretion of metabolic waste materials

2) Secretion, metabolism, and excretion of hormones

3) Water and electrolyte balance.

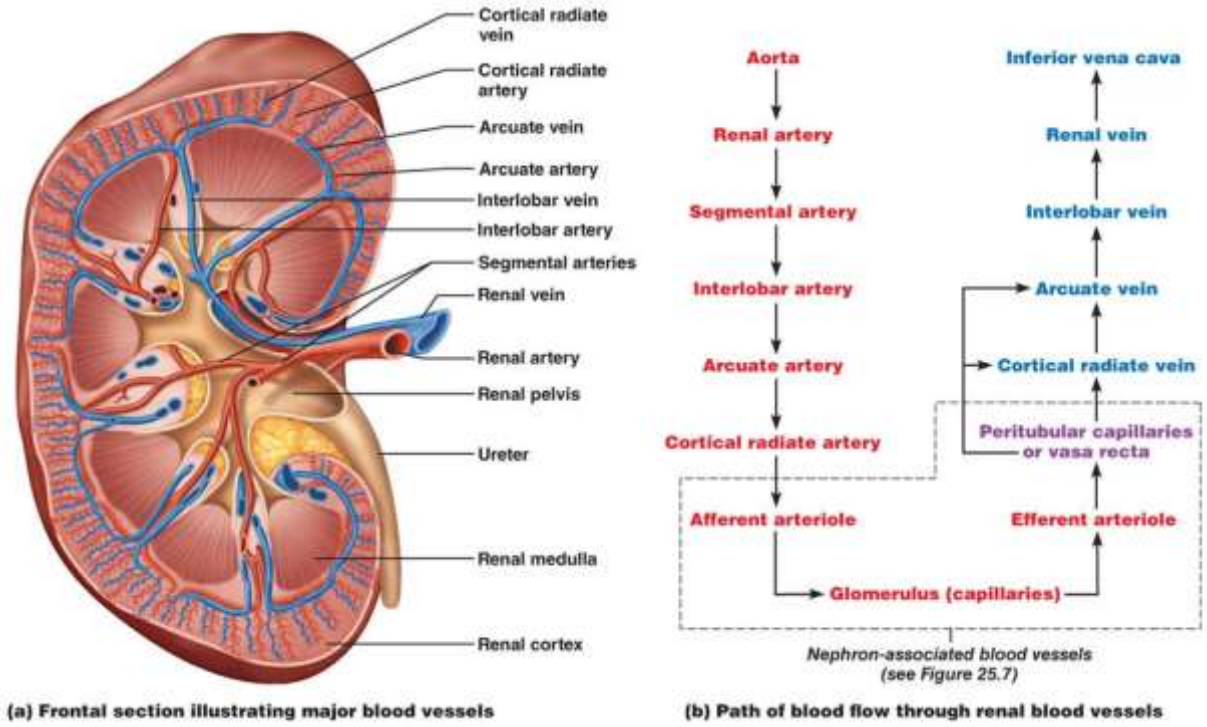
4) Acid base balance

5) Regulation of blood pressure

6) Gluconeogenesis

2.3.3. Renal Blood Supply

The kidneys receive 1.2 to 1.3 liters of blood or about 25% of the resting cardiac output [47]. Glomerulus receives capillaries from afferent arterioles.



Afferent arterioles are short straight branches of inter lobar arteries originating from renal artery a branch of abdominal aorta. Each afferent arteriole divides into multiple capillary branches. 20 to 50 such fenestrated capillary loops form glomerulus. Distal ends of the glomerular capillaries merge to form the efferent arteriole. Efferent arteriole forms peritubular capillaries that surround the renal tubule and emptying into renal vein.

A) Renal Blood Flow determinants

Renal blood flow is determined by the pressure difference between renal artery and renal vein divided by total renal vascular resistance.

$$\text{RBF} = \frac{Renal\ artery\ pressure - Renal\ vein\ pressure}{Total\ renal\ vascular\ resistance}$$

Renal arterial pressure is equal to systemic arterial pressure. Total renal vascular resistance is determined by summation of the resistances in the individual vessels including arteries, arterioles, capillaries and vein.

Though fluctuations in arterial pressure have some influence on renal blood flow, the kidneys have effective tools to maintain renal blood flow and GFR at fairly constant rate over a range between 80 and 170 mmHg of arterial pressure. This process is known as autoregulation. Mechanism of autoregulation is completely intrinsic to the kidney [28].

Intrinsic mechanism

The kidneys have intrinsic feedback mechanisms that usually keep the renal blood flow and glomerular filtration rate relatively constant, independent of systemic influences despite changes in arterial blood pressure. This is known as autoregulation [28]. The significance of autoregulation in tissues is to maintain the delivery of nutrients and oxygen at a normal level and to eliminate the waste products of metabolism, even when arterial pressure changes. Kidneys receive much higher blood flow than that required for these functions.

Extrinsic mechanisms

All blood vessels of the kidney, including afferent and efferent arterioles, are richly supplied by sympathetic nerve. Mild to moderate activation of

sympathetic activation has minor influence on renal blood flow and GFR. Whereas, when there is strong stimulation of the renal sympathetic plexus reduces the renal blood flow and GFR. For example, if there is sudden large drop in blood pressure due to hypovolemic shock sympathetic nervous system can override the renal autoregulation, constrict afferent arteriole and reduces GFR thereby. If still shock is not corrected the renin-angiotensin-aldosterone system gets activated, a hormone system which regulates blood pressure and fluid balance. *Another hormone,* atrial natriuretic peptide synthesized and secreted by myocytes of atrial wall when there is atrial stretching due to volume overload can *increase* the GFR and urine output.

Renal Circulation

Kidney receives 1.2 to 1.3 liter/ min blood (25% of cardiac output) at rest.

Renal plasma flow equals the amount of substance excreted per unit of time divided by arteriovenous difference for the substance across the kidney [30].

$$RPF = \frac{UcV}{S_{RAC} - S_{SVC}}$$

Where,

Uc = Concentration of substance in urine (mg/ml)

V = Urine flow (ml/min)

S_{RAC} & S_{SVC} = Substance renal arterial and venous concentrations respectively.

Renal plasma flow can be measured by infusing p- amino hippuric acid [31]. As excretion ratio is of PAH is high and its 90% is removed from artery in a single circulation through kidney and its renal arterial concentration is equal to plasma concentration. So renal plasma flow by PAH can also be measured by the formula known as effective renal plasma flow (EPRF).

$$ERPF = \frac{U_{PAH}\, V}{PAH\ plasma\ concentration}$$

2.3.4 Determination and Regulation of GFR

Normal GFR is 125 ml/min or 180 L/day. So kidney filters fluid equal to 4 times of total body water per day. GFR, like renal blood flow, remains constant over a wide range of perfusing pressure from 80 – 180 mmHg due to autoregulation. GFR is determined by changes in net filtration pressure and glomerular capillary co -efficient (K_f).

Net filtration pressure

It is sum of hydrostatic pressure and colloid osmotic pressure across glomerular capillary membrane. Factors favouring filtration are glomerular capillary hydrostatic pressure (P_G) and Bowman's capsule colloid osmotic pressure (π_G). Rise in glomerular capillary hydrostatic pressure increases GFR whereas, decrease in P_G reduces GFR. P_G is determined by arterial blood pressure,

afferent arteriolar resistance and efferent arteriolar resistance. Afferent arteriolar constriction caused by sympathetic stimulation or thromboxane A2 reduces hydrostatic pressure and GFR. Efferent arteriolar constriction caused by angiotensin II or ANP increase hydrostatic pressure and raises GFR. Efferent arteriolar constriction has a biphasic effect on GFR. Mild to moderate increase in resistance raises GFR but severe constriction decreases GFR. This is caused by nonlinear increase in colloid osmotic pressure by Donnan effect exceeding the P_G. Auto regulatory mechanisms buffer the effects of blood pressure and maintain relatively constant GFR. Opposing filtration are glomerular osmotic pressure and Bowman's capsule hydrostatic pressure.

Glomerular capillary filtration co- efficient is a product of hydraulic conductivity (permeability) and filtering surface area of glomerular capillaries.

$$K_f = \frac{GFR}{Net\ filtration\ pressure}$$

GFR is increased by raising K_f and decreased by reducing K_f , but changes in filtration co – efficient do not provide a primary mechanism for regulation of GFR.

Chronic uncontrolled hypertension and diabetes mellitus gradually decreases Glomerular capillary filtration co- efficient by increasing the glomerular basement membrane thickness. Increase in Bowman's capsule hydrostatic

pressure (eg: ureteric obstruction) oppose hydrostatic filtering pressure and filtration thereby decreases GFR.

Glomerular capillary colloid osmotic pressure is exerted by plasma proteins and tries to pull water into the circulation. So, it opposes filtration normally. Glomerular filtrate is essentially protein free because glomerular capillaries are relatively impermeable to proteins. This results in almost zero colloid osmotic pressure. Therefore glomerular oncotic pressure is much higher than that of glomerular filtrate in Bowman's capsule. Conditions causing fall in plasma protein concentration such as nephrotic syndrome and cirrhosis of liver decreases glomerular plasma oncotic pressure.

Water and electrolyte homeostasis by kidney

When the urine is dilute, water is excreted in excess of solutes. Conversely, when urine is concentrated, solutes are excreted in excess of water. Renal clearance is the rate at which plasma is cleared of water (free water clearance) and solutes (osmotic clearance) each minute. Osmotic clearance is calculated by dividing rate of osmotic clearance and plasma osmolarity.

$$Osmotic\ clearance = \frac{Urine\ osmolarity\ X\ Urine\ flow\ rate}{Plama\ osmolarity}$$

Antidiuretic hormone (ADH) a peptide hormone synthesized by hypothalamus, stored and secreted by posterior pituitary has impact on diluting and

concentrating ability of kidneys. Most important action of ADH on kidneys is to facilitate the permeability of collecting duct to water and to increase the permeability medullary collecting duct to urea. It also stimulates reabsorption of sodium chloride by thick ascending limb of loop of henle, distal tubule and collecting duct.

ADH exerts its antidiuretic effect by binding and activating vasopressin 2 receptors on basolateral membrane of principal cell of late distal tubule and collecting duct [33]. ADH binding to vasopressin 2 receptors increases cyclic AMP and stimulates protein kinase A eventually resulting in insertion aquaporin 2 (water channel) containing vesicles into the apical membrane of cell. With removal of ADH aquaporin channels are internalized into the cell and apical membrane again becomes impermeable to water. This transportation of water channels into and out of apical membrane regulates its permeability to water. Free water clearance is the volume of plasma cleared of solute free water each minute. It is calculated as the difference between water excretion and osmotic clearance [32]. It can be positive, negative or zero. Positive means kidneys are forming dilute urine. When water is removed from plasma in excess of solutes and plasma is being concentrated. In negative free water clearance urine

osmolarity is more than the plasma osmolarity indicating water conservation. In zero free water clearance kidneys produce urine osmotic to plasma.

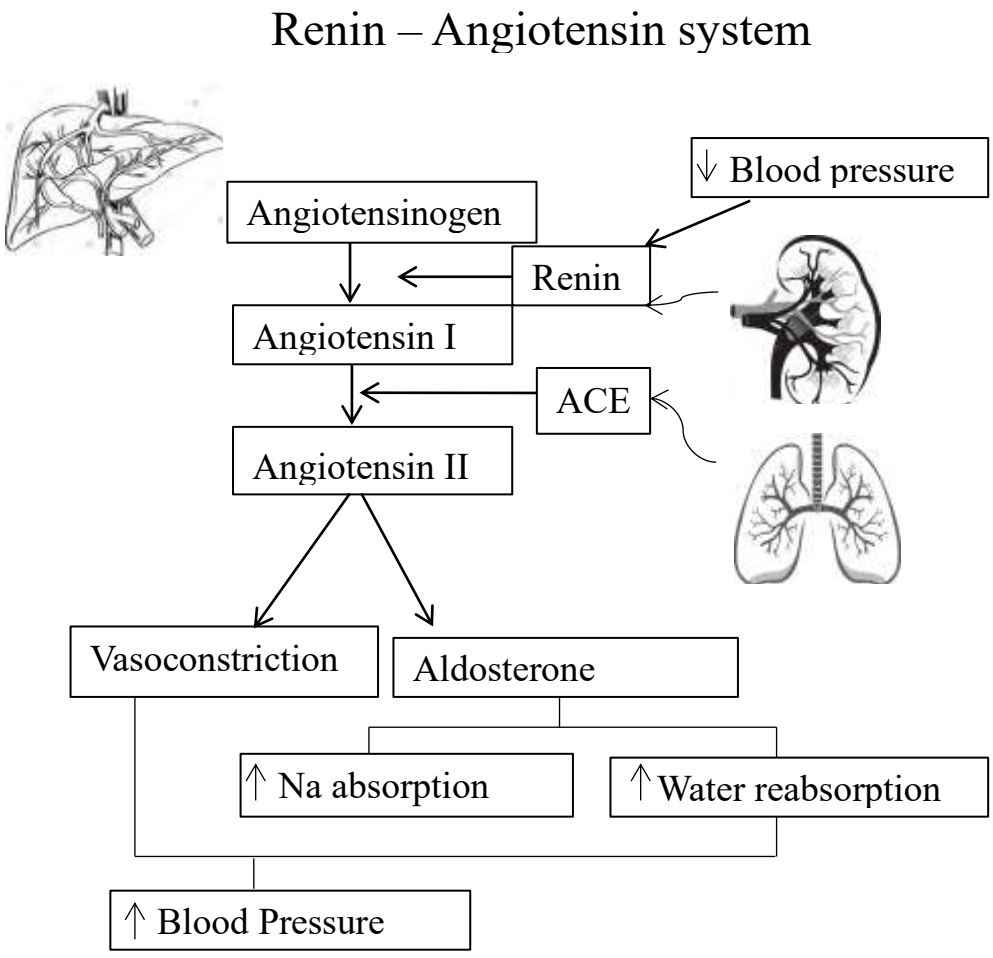
In addition to controlling total volume, the plasma **osmolarity** is also tightly regulated by kidneys. Extreme variation in osmolarity destroys cell structure and function. This is achieved by matching the intake and excretion of sodium with water. Regulation of osmolarity must be combined with regulation of volume, because changes in water volume alone have concentrating or diluting effects on the body fluids. If there is dehydration kidney excrete proportionately more water than solute, so that osmolarity of body fluid increases. Body must conserve water but not sodium. By increasing osmolarity, ADH and thirst mechanism comes into action, thus conserving water. If there is large amount of blood loss body should conserve both water and sodium.

Sodium reabsorption occurs in all segments of nephron except descending limb of loop of henle. Sodium is actively transported into the interstitium by Na+K+ATPase. Major portion (60%) of sodium reabsorption occurs in proximal convoluted tubule. About 7% of sodium absorption occurs in distal convoluted tubule for which aldosterone is needed. Aldosterone is secreted by adrenal cortex causes water and sodium reabsorption from distal convoluted tubule. ADH plays a major role in decreasing osmolarity by increasing water

reabsorption in the kidneys, thus dilutes body fluids. To avoid osmolarity from falling below normal, the kidneys also have a mechanism for reabsorbing sodium in the distal nephron. This mechanism is under the control of aldosterone**,** a steroid hormone secreted by the adrenal cortex. Aldosterone secretion is under the control of following mechanisms. When the **osmolarity** increases above normal, sensed by adrenal cortex which inhibits aldosterone secretion. In the absence of aldosterone less sodium is reabsorbed in the distal convoluted tubule. ADH secretion will also increase to conserve water, thus supplementing the effect of low aldosterone levels to reduce the osmolarity. The net effect is decreased urine output with more urine osmolarity.

Renin an acid protease which converts angiotensinogen to angiotensin I is secreted from distal convoluted tubule of kidney. Increased GFR reduces renin secretion. Angiotensin converting enzyme present in endothelium of lung capillaries converts angiotensin I into angiotensin II. It increases aldosterone secretion resulting in increased sodium and water reabsorption. It is a potent arteriolar constrictor resulting in rise in blood pressure and total peripheral resistance. In the kidney angiotensin II causes afferent arteriolar constriction, shrinkage of mesangial cells with resultant decrease in GFR [29]. It is dipsogenic , increases secretion of vasopressin(ADH) and ACTH and decreases renin secretion. In renal failure both these homeostatic mechanisms are

disturbed and severe abnormalities in fluid volume and electrolytes occur. There will be accumulation of fluid, acid, potassium and other waste products. Unless interventions have been initiated to restore renal function either completely or partially, death can occur.



2.3.5 Kidney diseases

Kidney diseases are among the most important cause of morbidity and mortality in many countries all over the world. Unfortunately, in India limited data available on the prevalence of CKD due to lack of proper longitudinal study. A

study published in Indian journal of nephrology in 2015 conducted from a rural belt of Karnataka was found that high prevalence of hypertension and renal disease in younger age groups (mean age was around 40 years) and low prevalence of diabetes mellitus surprisingly. Unfortunately, they found high prevalence (6.3%) of stage 3 chronic kidney disease which is the highest report till date [34]. Kidney diseases could be divided into Acute and Chronic Renal Failure.

i) Acute Renal Failure (ARF):

Acute renal failure is defined as a rapid, potentially reversible deterioration in renal function sufficiently enough to cause accumulation of nitrogenous waste products in the body results in [35]. (a) An increase in serum creatinine of ≥ 0.3 mg/ dl within 48 hours, or (b) An increase in serum creatinine of ≥ 1.5 times baseline which is known or presumed to have occurred within the prior seven days, or (c) Urine volume < 0.5 ml/ kg/ hour for more than six hours.

Presently, the term acute kidney injury (AKI) is often used in place of acute renal failure. The term ARF is used for the group of population who need dialysis support. RIFLE criteria are used to classify severity of AKI. RIFLE stands for Risk, Injury, Failure, Loss and End stage renal disease [36].

Table 5 RIFLE criteria

Stages	Glomerular filtration criteria/ serum creatinine	Urine output criteria
Risk	Increased s-creatinine x 1.5 or GFR decrease >25%	UO < 0.5 ml/kg/h for 6 hours
Injury	Increased s-creatinine x 2 or GFR decreased >50%	UO < 0.5 ml/kg/h for 12 hours
Failure	Increased s-creatinine x 3 or GFR decrease >75% or s-creatinine ≥320 µmol/l Acute rise ≥40 µmol/d	UO < 0.3 ml/kg/h for 24 hours (Oliguria) or Anuria x 12 hrs
	Dialysis dependence	
Loss	Persistent Acute Kidney Injury = complete loss of kidney function/dialysis dependent > 4 weeks	
End stage renal disease	End-stage renal disease/ dialysis dependent for >3 months	

Acute Kidney Injury Network (AKIN) classification: AKI is classified into three stages. (a) Stage 1 is same as Risk category of RIFLE with addition of increase in serum creatinine by 0.3 mg/ dl. (b) Stage 2 and 3 are same as Injury and Failure categories of RIFLE.

Acute renal failure is classified into (a) Prerenal – Kidneys are inadequately perfused either due to decreased cardiac output or loss of body fluid. GFR is greatly diminished resulting in oliguria. (b) Renal – Resulting from intrinsic diseases of the kidneys themselves, such as glomerular, tubulo-interstitial or vascular diseases. In acute tubular necrosis, a diminution in oxygen and nutrient supply to the tubular cells result in ischemia and necrosisof the tubular cells. Fortunately, the tubular cells can regenerate when causative factors are removed. (c) Post-renal: ARF is caused by an obstruction of the urinary tract at any point in its course.

In pre renal AKI patients usually presents with hypotension, poor peripheral perfusion and a falling urine output. ATN is the most important cause of ARF due to intrinsic renal disease. The clinical course of ATN can be divided into an oliguric phase, maintenance phase and a diuretic phase. Not all patients with ATN develop oliguric failure. Around 40% of the patients may have normal urine output. This is called non oliguric renal failure. The electrolyte disturbances are less in these patients. Patients with glomerulonephritis typically have hypertension, proteinuria and hematuria. Bilateral post renal obstruction commonly causes anuria. Patient can have loin pain, hematuria and renal colic. Patients with ARF due to any cause may also symptoms related to uremia.

Table 6 Causes of Acute Renal Failure

Pre Renal	Renal	Post Renal
1. Hypovolemia due to diarrhoea, fever and bleeding 2. Cardiac Failure 3.Hepatorenal syndrome 4.Renal artery occlusion 5. Rhabdomyolysis 6. Haemolysis 7. Severe sepsis	1. Glomerulonephritis including vasculitis 2. Interstitial nephritis due to infections, drugs, intoxications 3.Hereditary disturbances such as Polycystic kidney disease (acute bleeding) 4. Transplant kidney rejection	1. Prostatic obstruction 2. Urinary tract obstruction (tumour, blood clots or stones) 3. Urinary retention due to dysfunction in detrusor by drugs and denervation 4. Pyelonephritis and urosepsis

These include anorexia, nausea, vomiting, pruritis, uremic encephalopathy and dyspnea due to fluid overload. In acute kidney injury haemoglobin is usually normal, and the kidneys size may be normal or large. Biomarkers are available to diagnose AKI early [38]. These are gelatinase – associated lipocalin (NGAL), kidney injury molecule – 1(KIM-1), interlukin18 and cystatin C.

Management of AKI: Therapy for AKI is directed at correcting fluid and electrolyte abnormalities, treating the underlying cause and preventing

complications including nutritional deficiencies. An attempt should be made to identify the cause and to correct it if possible. Administer a challenge of fluid intravenously in patients with clinical history consistent with fluid loss and physical examination consistent with hypovolemia. Emergency treatment should be started for hyperkalemia to prevent life threatening complications. Acidosis should be treated with intravenous or oral bicarbonate if serum bicarbonate level is < 15 mEq/L. After correction of fluid deficit, maintain a daily fluid intake equal to the amount of urine output plus 400 – 500 ml to balance the insensible loss. Dietary protein should be constrained to about 40 g/ day. Attempts can be made to suppress endogenous protein catabolism to a minimum by giving as much energy as possible in the form of carbohydrates and fats. Salt should also be restricted. Nephrotoxic drugs should be avoided. Patients with RPGN are treated with corticosteroids and cyclophosphamide. If conservative measures fail, hemodialysis may be required.

1. Indications of Hemodialysis
2. Symptomatic uremia with high blood urea
3. Resistant hyperkalemia
4. Uremic pericarditis
5. Refractory pulmonary edema
6. Severe metabolic acidosis

7. Uremic encephalopathy

Patients recovered from acute kidney injury should be followed up periodically [38], because an episode of AKI can increase the risk of developing chronic kidney disease and other cardiovascular complications such as myocardial infarction and cerebrovascular accident in future. Many studies found that AKI patients not only having increased risk of future cardiovascular complications, mortality is also high in patients having myocardial infarction along with renal dysfunction. Though acute cerebrovascular accident is a common disease and shares the similar atherosclerotic risk factors with ischemic heart disease, the association of stroke and renal function is poorly investigated.

ii) Chronic Kidney Disease

Chronic kidney disease is defined as GFR < 60 ml/ min/ 1.73 m2 body surface areas due to abnormalities of kidney structure or function, present more than 3 months with implications for health [48]. Kidney damage for ≥ 3months with or without decreased GFR, as evidenced by any of the following:

1. Microalbuminuria (urine albumin excretion 30 – 300 mg/ day)
2. Macroalbumiuria (urine albumin > 300 mg/ day)
3. Persistent hematuria (where other causes such as urologic conditions have been excluded)

4. Urine sediment abnormalities
5. Electrolyte abnormalities
6. Radiological abnormalities such as scarring or polycystic kidneys on ultrasound
7. Abnormal renal biopsy
8. History of transplantation

Major outcomes of renal dysfunction are progression of kidney failure, complications from decreased kidney function and development of cardiovascular disease including stroke. Cardiovascular events are more common than renal failure. The purpose of the present study is to investigate the role of renal function in patients with acute stroke on overall outcome. Therapeutic interventions in the earlier stages may prevent or reduce some of these complications including progression to kidney failure. Risk factors for developing renal dysfunction are older age, family history of kidney disease, poor glycemic control in diabetes mellitus, hypertension, autoimmune disease, systemic infections, UTI, obstructive uropathy, nephrotoxic drugs and smoking.

2.3.6 Assessment of renal function

Usually renal function has been assessed by blood urea and serum creatinine in daily clinical practice. However, these investigations do not give an accurate measure of the renal clearance as glomerular filtration rate (GFR).

Urea: Urea is the principle waste product of protein and amino acid metabolism.

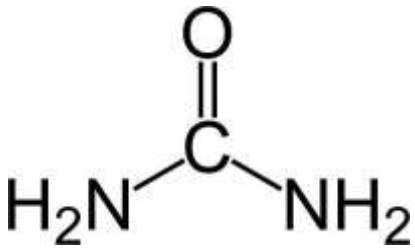


Fig 6 Molecular formula of urea

Proteins are metabolized into amino acids, which are consecutively deaminated with production of ammonia which is toxic. Then ammonia is entered into a series of reactions in hepatocytes known as urea cycle and converted into less toxic urea which is excreted mostly by kidneys. Increased urea production is associated with increased protein catabolism such as diet rich in protein, tissue protein breakdown during starvation or any other pathology. Urea is both secreted and reabsorbed in renal tubule. So, the net effect is around 30 – 40% of the filtered urea appears in urine.

Blood Urea Nitrogen: Molecular weight of urea ($CO(NH_2)2$ is 60 (C -12, 2N – 28, O – 16, 4H - 4). Only nitrogen content of urea known as blood urea nitrogen (MW – 28) is approximately half of the urea.

Creatinine: Creatine is an endogenously formed molecule that is stored mainly in skeletal muscle, in both free and phosphorylated forms. The phosphorylated form is named as creatine phosphate.

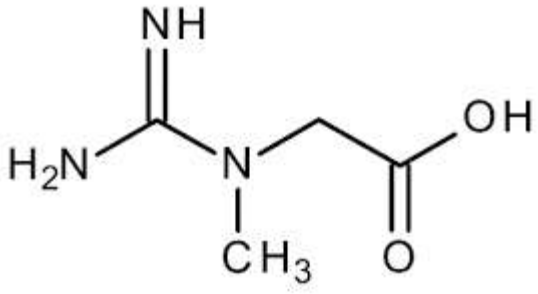


Fig 7 Molecular formula of creatinine

Creatinine is a non-protein nitrogenous breakdown constituent of creatine phosphate produced in kidney, liver and pancreas. Generally it is synthesized at a fairly constant rate depending on muscle mass and excreted predominantly by the kidneys by glomerular filtration and tubular secretion. Little or no tubular reabsorption. If there is defect in renal filtration serum creatinine levels will be increased. Serum creatinine is most commonly used investigation to assess the renal function. But this may not be accurate due to various reasons like age, sex, race and body mass.

eGFR Estimation

Measuring GFR is challenging to perform practically which has been explained in previous chapter. Hence, eGFR is often derived from serum creatinine using following equations [49, 50].

$$MDRD\ eGFR = 186 \times [\ Plasma\ Creatine\ (\mu mol/L) \times 0.0011312]^{-1.154} \times [\ age(years)]^{-0..203} \times [0.742\ if\ female] \times [1.212\ if\ black]$$

$$MDRD\ eGFR(IDMS\ aligne) = 175 \times [\ Plasma\ Creatine\ (\mu mol/L) \times 0.0011312]^{-1.154} \times [\ age(years)]^{-0..203} \times [0.742\ if\ female] \times [1.212\ if\ black]$$

$CKD - EPI\ eGFR$;

$$Female\ with\ Creatine < 62\ (\mu mol/L); use\ eGFR = 144 \times (Cr/61.6)^{-0.329} \times (0.993)^{age}$$

$$Female\ with\ Creatine > 62\ (\mu mol/L); use\ eGFR = 144 \times (Cr/61.6)^{-1.209} \times (0.993)^{age}$$

$$Male\ with\ Creatine < 80\ (\mu mol/L); use\ eGFR = 141 \times (Cr/79.2)^{-0.411} \times (0.993)^{age}$$

$$Male\ with\ Creatine > 80\ (\mu mol/L); use\ eGFR = 141 \times (Cr/79.2)^{-1.209} \times (0.993)^{age}$$

2.3.6 Unrecognized renal dysfunction

Though renal dysfunction has clinically significant impact on outcome of cardiovascular disorders, it is often missed because renal function is assessed routinely by serum creatinine. A significant percentage of patients with normal serum creatinine levels or slightly above the normal range have reduced renal function, which may often be clinically significant. Hence, the term unrecognized renal dysfunction, is defined as an estimated glomerular filtration rate <60 mL/min/1.73 m2 in the presence of normal serum creatinine. This is a common comorbidity among patients with various cardiovascular diseases including stroke (ischemic and hemorrhagic) which has not been studied extensively. Unrecognized renal insufficiency has also been strongly associated with adverse outcomes in patients with cardiovascular disorders [2]. This is more frequently seen in elderly and females patients. This can be explained by

the frailty and lower muscle mass of these patients that may result in significant renal dysfunction with normal serum creatinine levels.

2.4 Renal dysfunction and cerebrovascular accident

Chronic kidney disease stage ≥2 is an important risk factor for cardiovascular diseases including stroke. The Cardiovascular Health Study has shown that patients aged more than 65 years with raised serum creatinine were associated with greater mortality from cardiovascular disease compared to patients with normal creatinine (3.6% vs 1.3%) [1]. HOPE study has reported that even mild renal dysfunction was associated with increased risk of stroke. Furthermore, reduced eGFR was associated with increased risk of death and cardiovascular events. On the other hand, renal dysfunction may correlate with endothelial dysfunction since patients with chronic kidney disease stage 5 have increased arterial stiffness which in turn is an independent risk factor for atherosclerosis [3]. Even mild to moderate renal dysfunction is associated with central artery stiffness, signifying that renal insufficiency adversely affect small and large arteries. Epidemiological study demonstrated that renal insufficiency forecast long-term mortality and hence can be used to stratify risk for stroke patients. A stroke treatment guideline recommends that urea and creatinine values are important in the acute condition [3, 1, 2]. Latest study involved 7900 patients with acute stroke included in the prospective National Acute Stroke ISraeli

registry established that unrecognized renal dysfunction is more common and is associated with adverse short term outcomes among patients with acute stroke [2]. This study also reported mortality rates are higher in patients with unrecognized and recognized renal insufficiency compared with patients with normal renal function (9.1%, 9.9%, and 4.4%, respectively). However, the outcome of stroke patients whether improves with intervention to prevent or treat renal dysfunction is not yet known.

AIMS AND OBJECTIVES

The aim of this study is

To determine the prevalence of the unrecognized renal insufficiency in patients admitted with acute stroke and its clinical significance.

To evaluate role of unrecognized renal insufficiency as a risk factor contributing to short term mortality.

MATERIAL & METHODS

Study design: Cross sectional study

Study center: Stanley Government Medical College, Chennai

Study duration: March 2017 to August 2017

Inclusion criteria: All patients admitted with acute stroke

Exclusion criteria: Acute stroke in < 18 years

Head injury

Methodology:

The study group consisted of 100 patients with acute stroke admitted in Stanley Govt. Medical College. Stroke is defined as abrupt onset of neurological deficit.

The detailed history of the patients has been recorded and patients underwent a detailed clinical examination.

Hemogram, Metabolic profile, chest radiography, ecg and brain imaging (CT / if needed MRI brain) were done in all patients.

The estimated glomerular filtration rate is calculated using the simplified Modification of Diet in Renal Disease formula and Chronic Kidney Disease Epidemiology Collaboration equation.

The study groups are stratified into 3 groups according to the renal function assessment (normal renal Function, unrecognized renal insufficiency, and recognized renal insufficiency).

Unrecognized renal insufficiency is defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2 in the presence of serum creatinine 1.2 mg/dL.

MDRD formula:

186×[serum creatinine (mg/ dl)] – 1.154×[age in years]– 0.203.

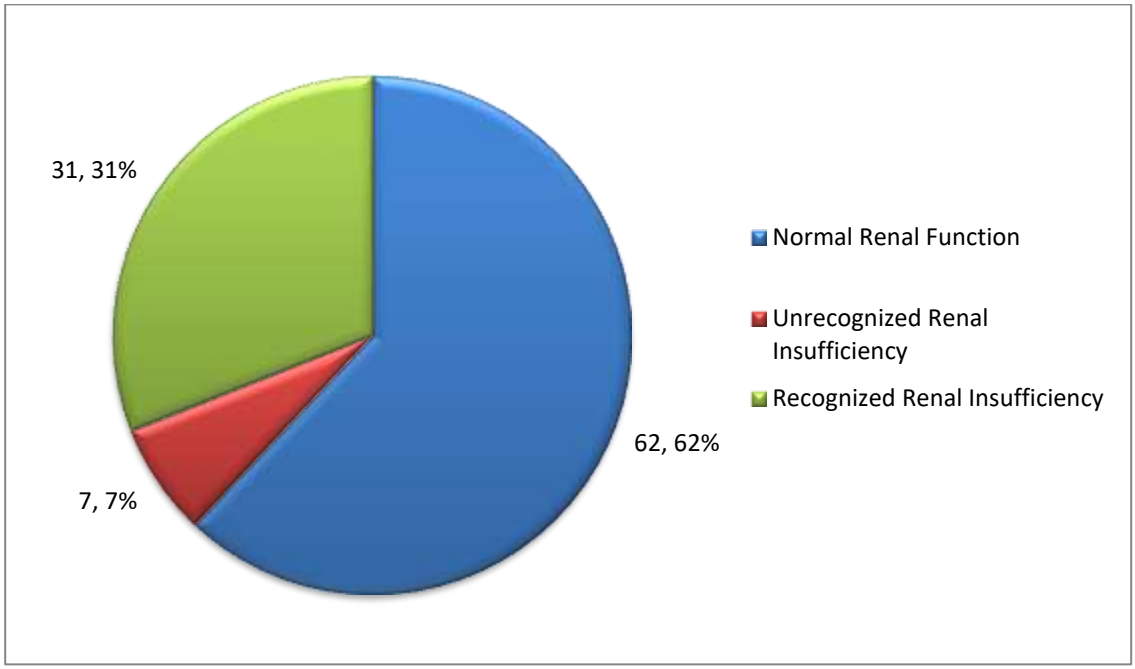
For women, the product of this equation was multiplied by a factor of 0.742.

The two primary outcomes are in-hospital mortality and severe disability at discharge in 3 groups are estimated and compared within 3 groups.

Ethical Committee Approval: Approval was obtained for this study.

RESULT AND DISCUSSION

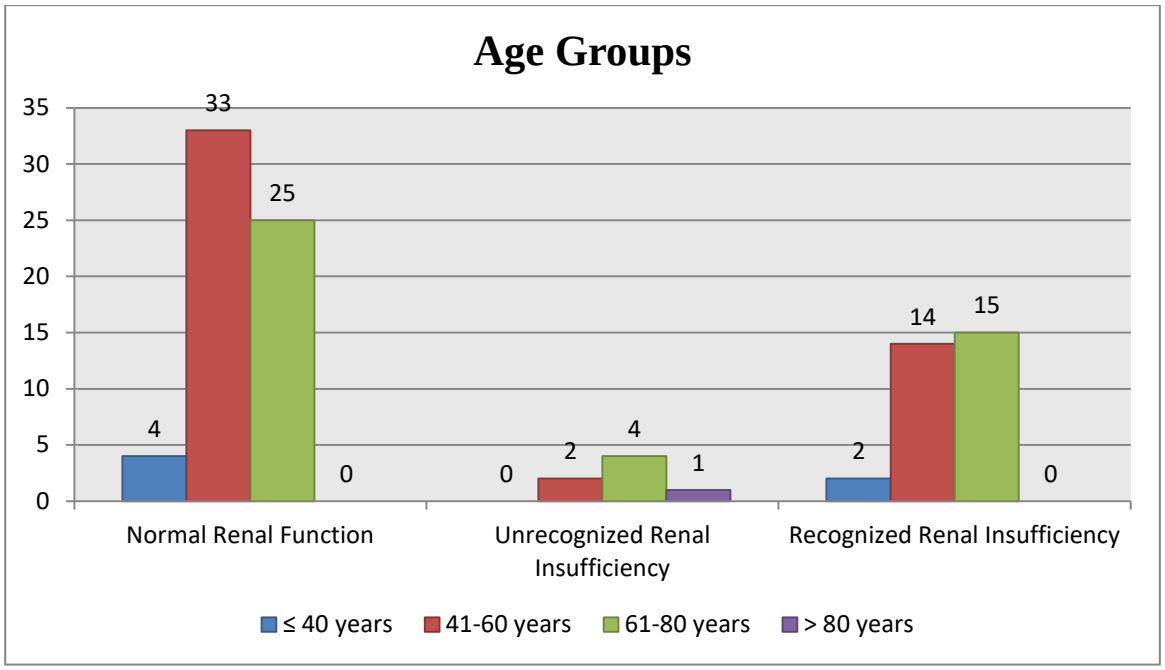
Study Subjects



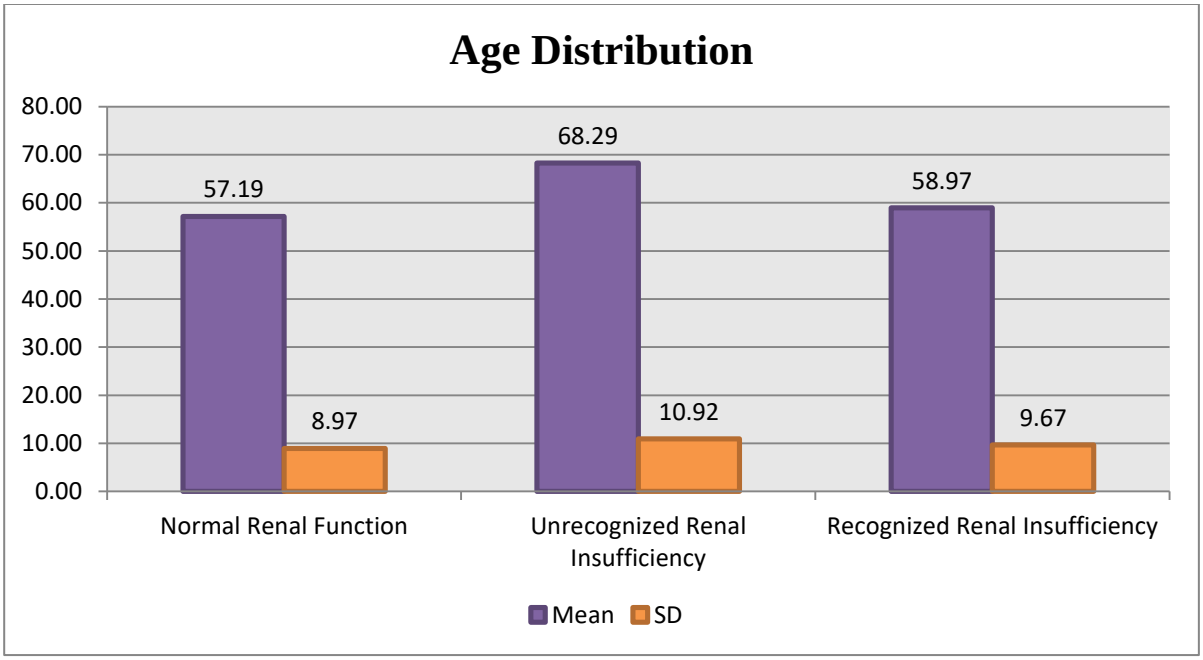
Study Subjects	Normal Renal Function	Unrecognized Renal Insufficiency	Recognized Renal Insufficiency
Number	62	7	31
Percentage	62%	7%	31%

Out of the 100 patients with acute stroke included in the study, 62 (62%) have normal renal function, 31 (31%) have recognized renal insufficiency, and 7 (7%) have unrecognized renal insufficiency.

Age



Age Groups	Normal Renal Function	%	Unrecognized Renal Insufficiency	%	Recognized Renal Insufficiency	%
≤ 40 years	4	6.45	0	0.00	2	6.45
41-60 years	33	53.23	2	28.57	14	45.16
61-80 years	25	40.32	4	57.14	15	48.39
> 80 years	0	0.00	1	14.29	0	0.00
Total	62	100.00	7	100.00	31	100.00



Age Distribution	Normal Renal Function	Unrecognized Renal Insufficiency	Recognized Renal Insufficiency
Mean	57.19	68.29	58.97
SD	8.97	10.92	9.67
P value Single Factor ANOVA Test			0.0135

Results

While analyzing age distribution in relation to renal function among stroke patients, it was observed that majority of the study subjects in normal renal function group were distributed in 41-60 years age group (n=33, 53.23%), 61-80 years age group in unrecognized renal insufficiency group (n=4, 57.14%) and recognized renal insufficiency group (n=15, 48.39%).

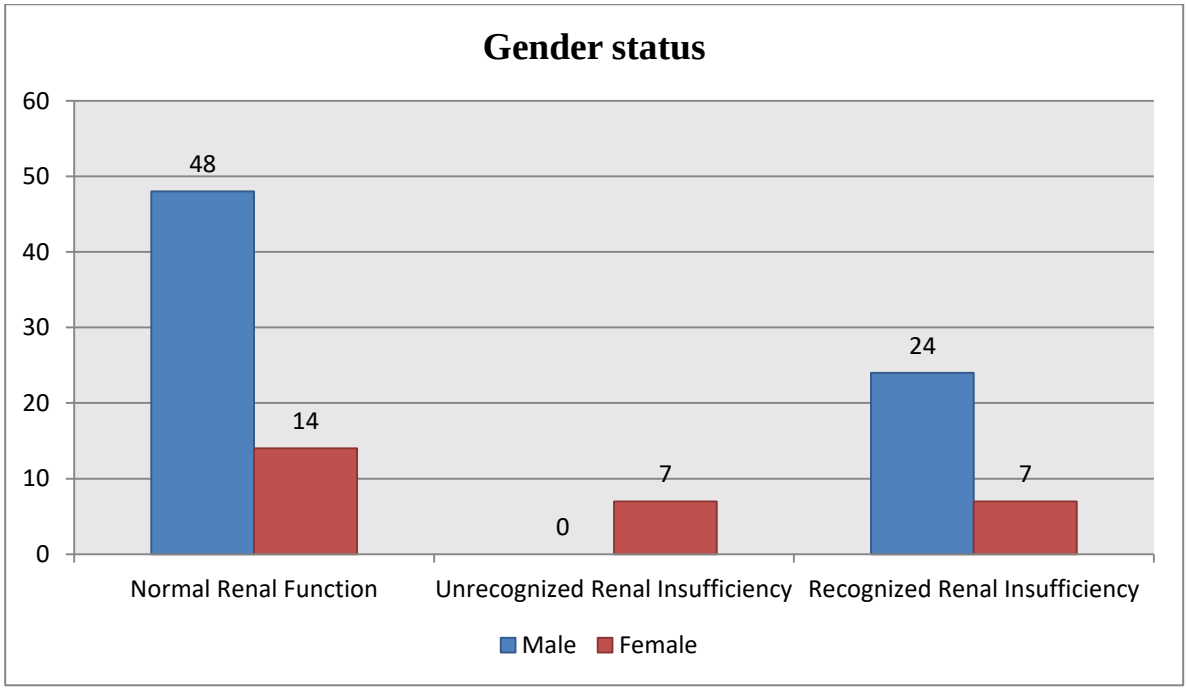
Discussion

When the age distribution between three groups was analysed statistically using single factor ANOVA test, the difference in the mean age of patients in normal renal function group (57.19), unrecognized renal insufficiency group (68.29) and recognized renal insufficiency group (58.97) was found to be statistically significant ($p < 0.05$).

Conclusion

We can conclude that unrecognized renal insufficiency among stroke patients is found significantly common among older age group in our study group.

Gender



Gender status	Normal Renal Function	%	Unrecognized Renal Insufficiency	%	Recognized Renal Insufficiency	%
Male	48	77.42	0	0.00	24	77.42
Female	14	22.58	7	100.00	7	22.58
Total	62	100.00	7	100.00	31	100.00
P value Fishers Exact Test				<0.0001		

Results

While analyzing gender status in relation to renal function among stroke patients, it was observed that majority of the study subjects in normal renal function group were males (n=48), females in unrecognized renal insufficiency group (n=7) and males in recognized renal insufficiency group (n=24).

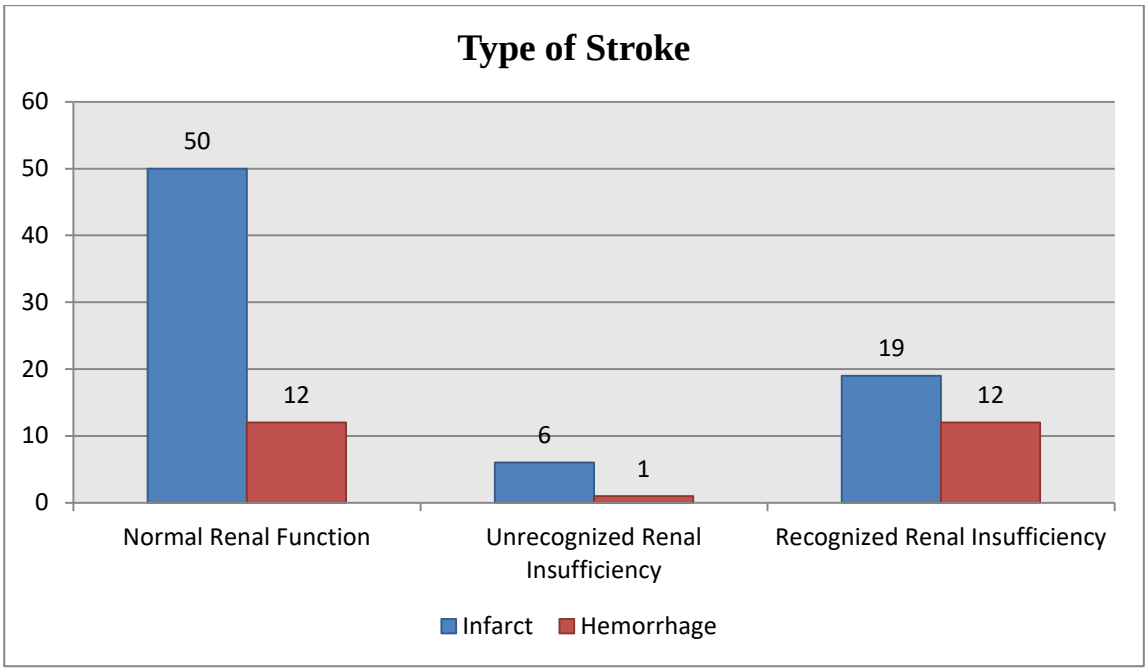
Discussion

When the gender status between three groups was analysed statistically using fishers exact test, the difference in percentage of females in normal renal function group (22.58%), unrecognized renal insufficiency group (100.00%) and recognized renal insufficiency group (22.58%) was found to be statistically significant ($p < 0.05$). it is evident that there is a statistically significant increase in incidence of unrecognized renal insufficiency in females compared to males.

Conclusion

We can conclude that unrecognized renal insufficiency among stroke patients is found significantly common among females compared to males in our study group.

Type of Stroke



Type of Stroke	Normal Renal Function	%	Unrecognized Renal Insufficiency	%	Recognized Renal Insufficiency	%
Infarct	50	80.65	6	85.71	19	61.29
Hemorrhage	12	19.35	1	14.29	12	38.71
Total	62	100.00	7	100.00	31	100.00
P value Fishers Exact Test				0.1171		

Results

While analyzing type of stroke in relation to renal function among stroke patients, it was observed that majority of the study subjects had infarct in normal renal function group (n=50), in unrecognized renal insufficiency group (n=6) and in recognized renal insufficiency group (n=19).

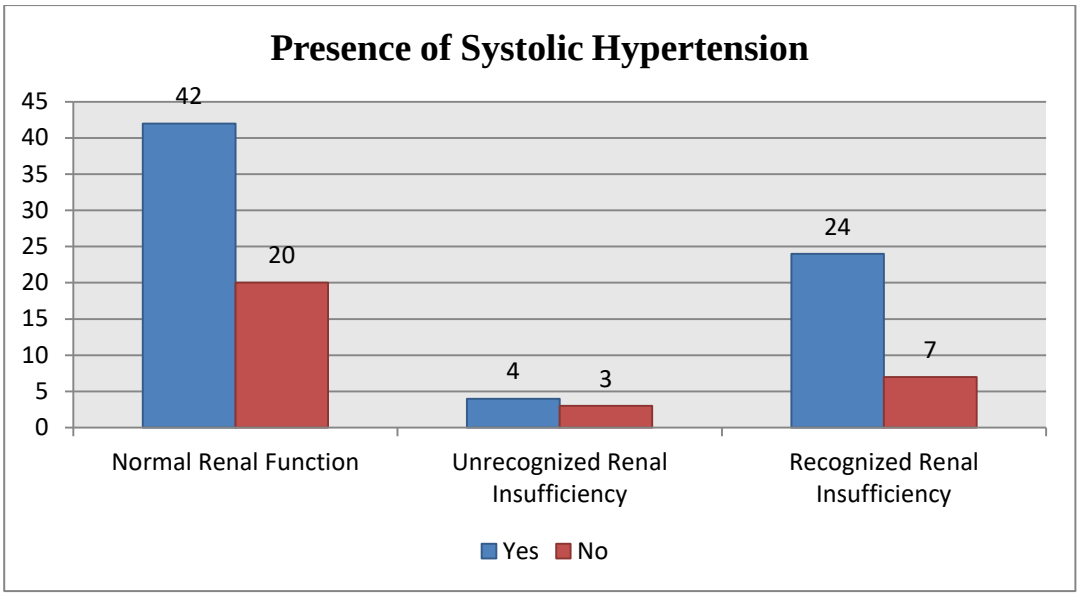
Discussion

When the type of stroke between three groups was analysed statistically using fishers exact test, the difference in percentage of infarct type in normal renal function group (80.65%), unrecognized renal insufficiency group (85.71%) and recognized renal insufficiency group (61.29%) was found to be statistically insignificant ($p > 0.05$).

Conclusion

In a study conducted in Medical University of Bialystok, Poland found that patients with hemorrhagic stroke experienced more worsening of renal function compared to ischemic stroke [1]. But in our study we found that variable type of stroke is normally distributed across the three study groups and has no bearing on renal function among stroke patients.

Systolic Hypertension



Presence of Systolic Hypertension	Normal Renal Function	%	Unrecognized Renal Insufficiency	%	Recognized Renal Insufficiency	%
Yes	42	67.74	4	57.14	24	77.42
No	20	32.26	3	42.86	7	22.58
Total	62	100.00	7	100.00	31	100.00
P value Fishers Exact Test				0.4631		

Results

While analyzing incidence of hypertension in relation to renal function among stroke patients, it was observed that majority of the study subjects had hypertension in normal renal function group (n=42), in unrecognized renal insufficiency group (n=4) and in recognized renal insufficiency group (n=24).

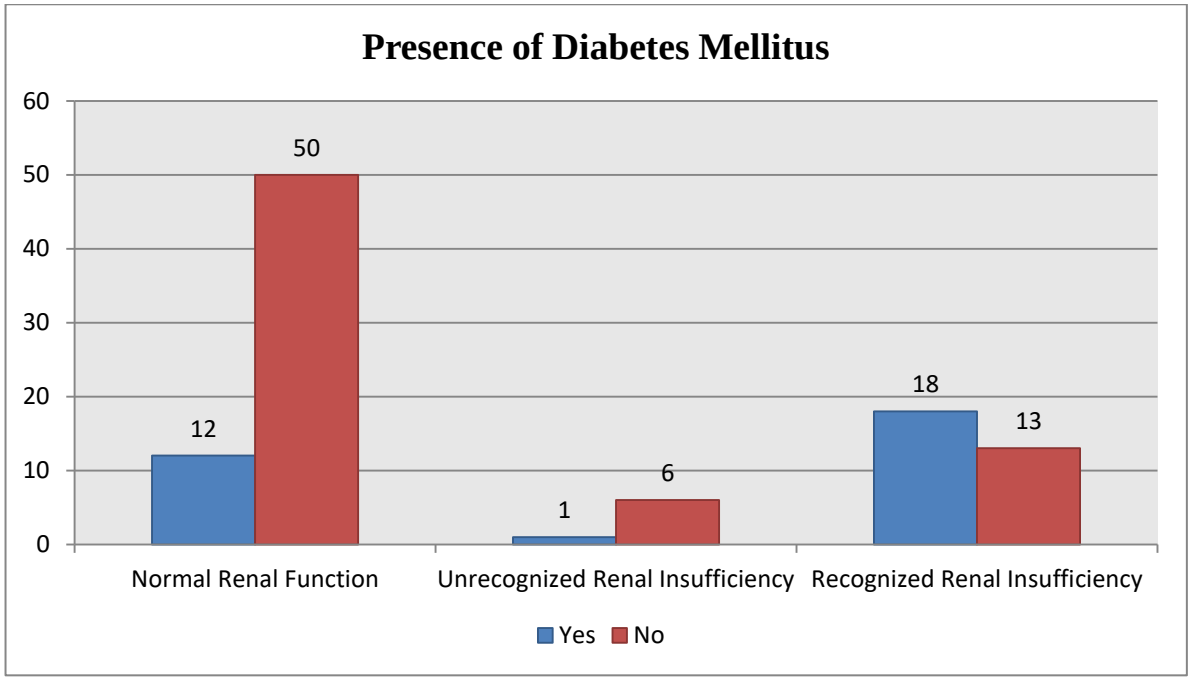
Discussion

When the hypertension status between three groups was analysed statistically using fishers exact test, the difference in percentage of subjects with hypertension in normal renal function group (67.64%), unrecognized renal insufficiency group (57.14%) and recognized renal insufficiency group (77.42%) was found to be statistically insignificant (p >0.05).

Conclusion

We can conclude that the variable hypertension is normally distributed across the three study groups and has no bearing on renal function among stroke patients.

Diabetes Mellitus



Presence of Diabetes Mellitus	Normal Renal Function	%	Unrecognized Renal Insufficiency	%	Recognized Renal Insufficiency	%
Yes	12	19.35	1	14.29	18	58.06
No	50	80.65	6	85.71	13	41.94
Total	62	100.00	7	100.00	31	100.00
P value Fishers Exact Test				0.0005		

Results

While analyzing incidence of diabetes mellitus in relation to renal function among stroke patients, it was observed that majority of the study subjects were non diabetics in normal renal function group (n=50) and in unrecognized renal insufficiency group (n=6) and diabetics in recognized renal insufficiency group (n=18).

Discussion

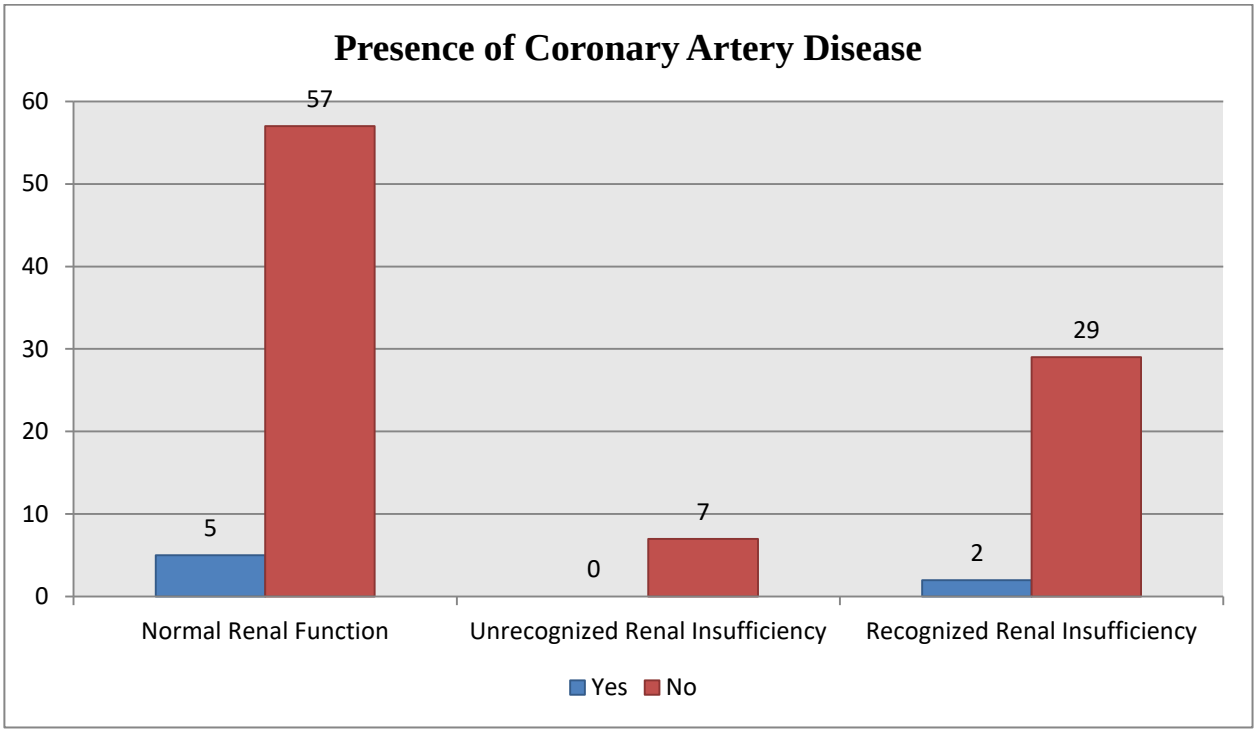
When the diabetes mellitus status between three groups was analysed statistically using fishers exact test, the difference in percentage of diabetics in normal renal function group (19.35%), unrecognized renal insufficiency group (14.29%) and recognized renal insufficiency group (58.06%) was found to be statistically significant ($p < 0.05$). It is evident that there is a statistically significant increase in incidence of diabetes in recognized renal insufficiency

group compared to normal renal function group (67% increase) and unrecognized renal insufficiency group (75% increase)

Conclusion

We can conclude that recognized renal insufficiency among stroke patients is found significantly common among diabetics in our study group.

Coronary Artery Disease



Presence of Coronary Artery Disease	Normal Renal Function	%	Unrecognized Renal Insufficiency	%	Recognized Renal Insufficiency	%
Yes	5	8.06	0	0.00	2	6.45
No	57	91.94	7	100.00	29	93.55
Total	62	100.00	7	100.00	31	100.00
P value Fishers Exact Test				>0.9999		

Results

While analyzing incidence of coronary artery disease in relation to renal function among stroke patients, it was observed that majority of the study subjects had no coronary artery disease in normal renal function group (n=57), in unrecognized renal insufficiency group (n=7) and in recognized renal insufficiency group (n=29).

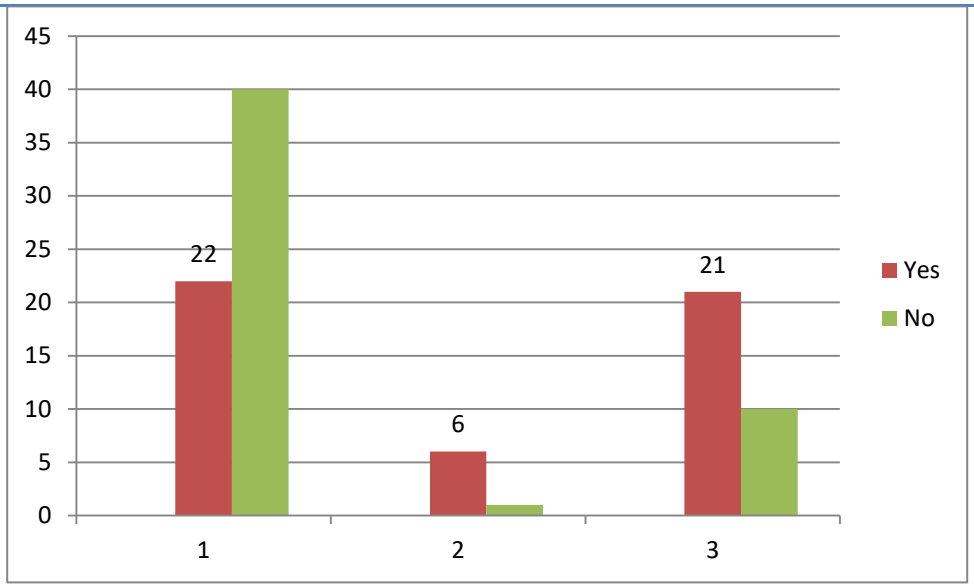
Discussion

When the coronary artery disease status between three groups was analysed statistically using fishers exact test, the difference in percentage of subjects with coronary artery disease in normal renal function group (8.00%), unrecognized renal insufficiency group (0.00%) and recognized renal insufficiency group (6.45%) was found to be statistically insignificant ($p > 0.05$).

Conclusion

In our study we found that prevalence of coronary artery disease is low (7%) and it is normally distributed across the three study groups and has no bearing on renal function among stroke patients.

Dyslipidemia



Dyslipidemia Status	Normal Renal Function	%	Unrecognized Renal Insufficiency	%	Recognized Renal Insufficiency	%
Yes	22	35.48	6	85.71	21	67.74
No	40	64.51	1	14.28	10	32.25
Total	62	100.00	7	100.00	31	100.00
P value Fishers Exact Test				0.0014		

Results

While analyzing incidence of dyslipidaemia in relation to renal function among stroke patients, it was observed that majority of the study subjects had dyslipidaemia in normal renal function group (n=22), in unrecognized renal insufficiency group (n=6) and in recognized renal insufficiency group (n=21).

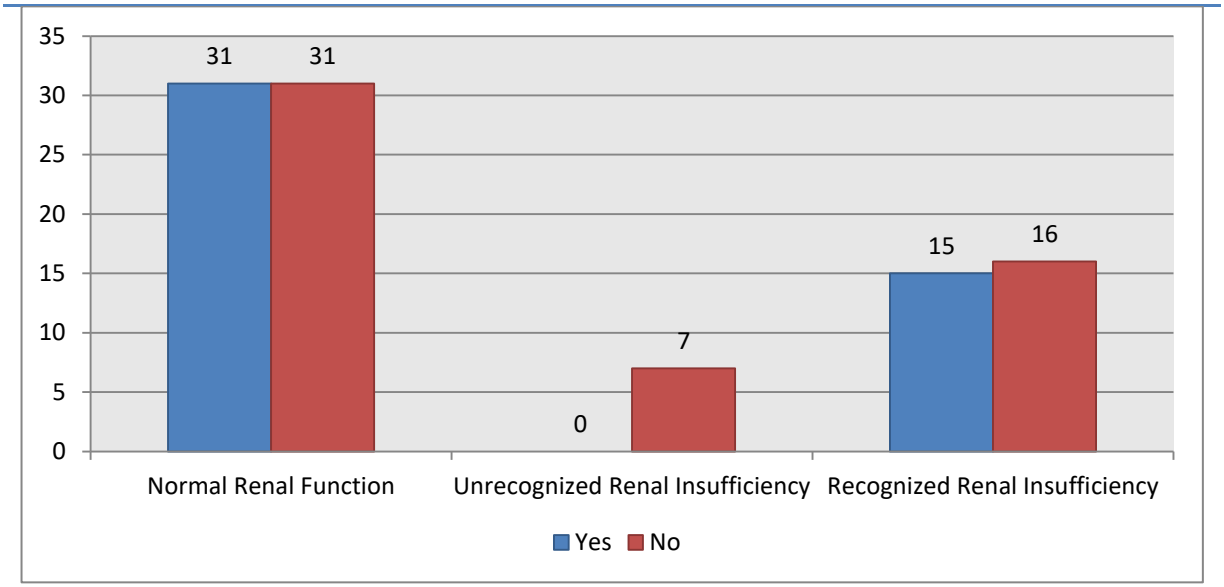
Discussion

When the dyslipidemia status between three groups was analysed statistically using fishers exact test, the difference in percentage of subjects with dyslipidemia in normal renal function group (35.48%), unrecognized renal insufficiency group (85.71%) and recognized renal insufficiency group (67.74%) was found to be statistically significant ($p < 0.05$).

Conclusion

We can conclude that dyslipidemia among stroke patients is found significantly common in both unrecognized and recognized renal insufficiency compared with patients having normal renal function in our study group.

Smoking Status



Smoking Status	Normal Renal Function	%	Unrecognized Renal Insufficiency	%	Recognized Renal Insufficiency	%
Yes	31	50.00	0	0.00	15	48.39
No	31	50.00	7	100.00	16	51.61
Total	62	100.00	7	100.00	31	100.00
P value Fishers Exact Test				0.3051		

Results

While analyzing incidence of smoking in relation to renal function among stroke patients, it was observed that majority of the study subjects were non smokers in normal renal function group (n=31), in unrecognized renal insufficiency group (n=7) and in recognized renal insufficiency group (n=16).

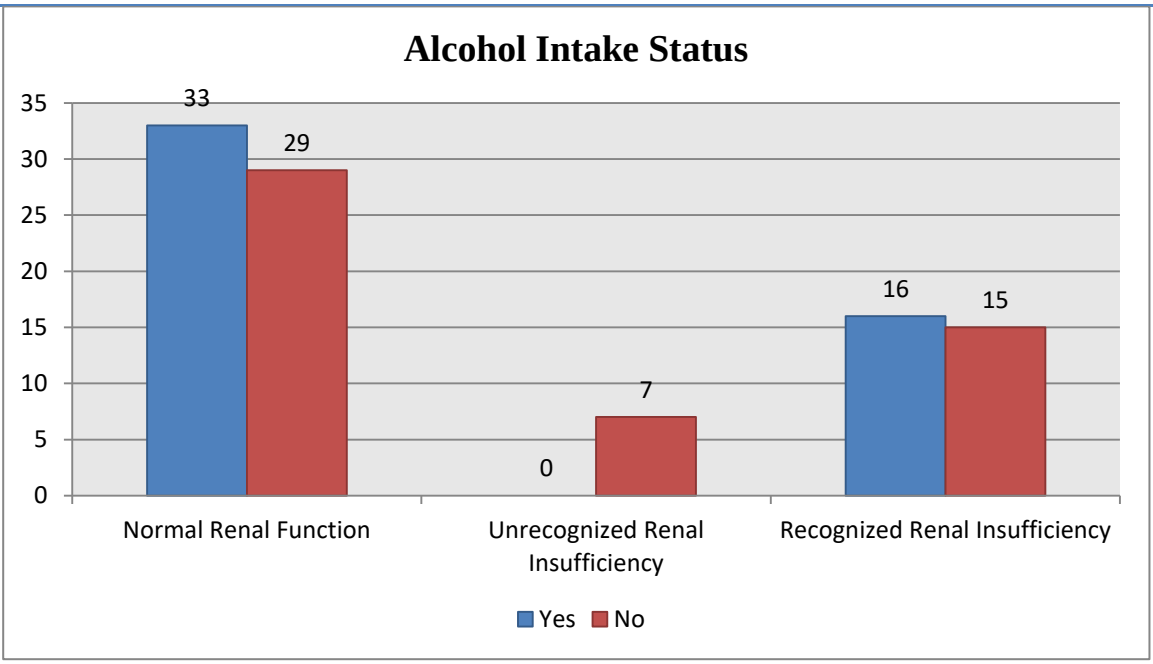
Discussion

When the smoking status between three groups was analysed statistically using fishers exact test, the difference in percentage of subjects with smoking habit in normal renal function group (50.00%), unrecognized renal insufficiency group (0.00%) and recognized renal insufficiency group (48.39%) was found to be statistically insignificant ($p > 0.05$).

Conclusion

We can conclude that the variable smoking is normally distributed across the three study groups. Hence, relation between smoking and renal dysfunction is statistically insignificant in our study.

Alcohol Intake



Alcohol Intake Status	Normal Renal Function	%	Unrecognized Renal Insufficiency	%	Recognized Renal Insufficiency	%
Yes	33	53.23	0	0.00	16	51.61
No	29	46.77	7	100.00	15	48.39
Total	62	100.00	7	100.00	31	100.00
P value Fishers Exact Test					0.2334	

Results

While analyzing incidence of alcohol intake in relation to renal function among stroke patients, it was observed that majority of the study subjects were alcoholics in normal renal function group (n=33), in recognized renal insufficiency group (n=16) and non-alcoholics in unrecognized renal insufficiency group (n=7).

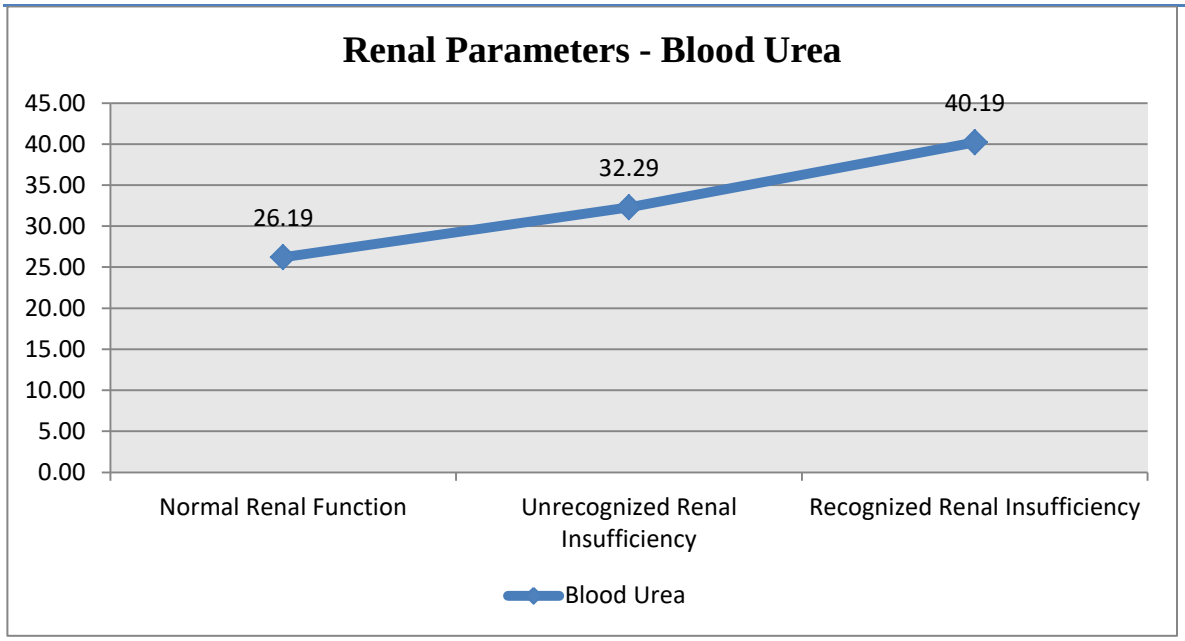
Discussion

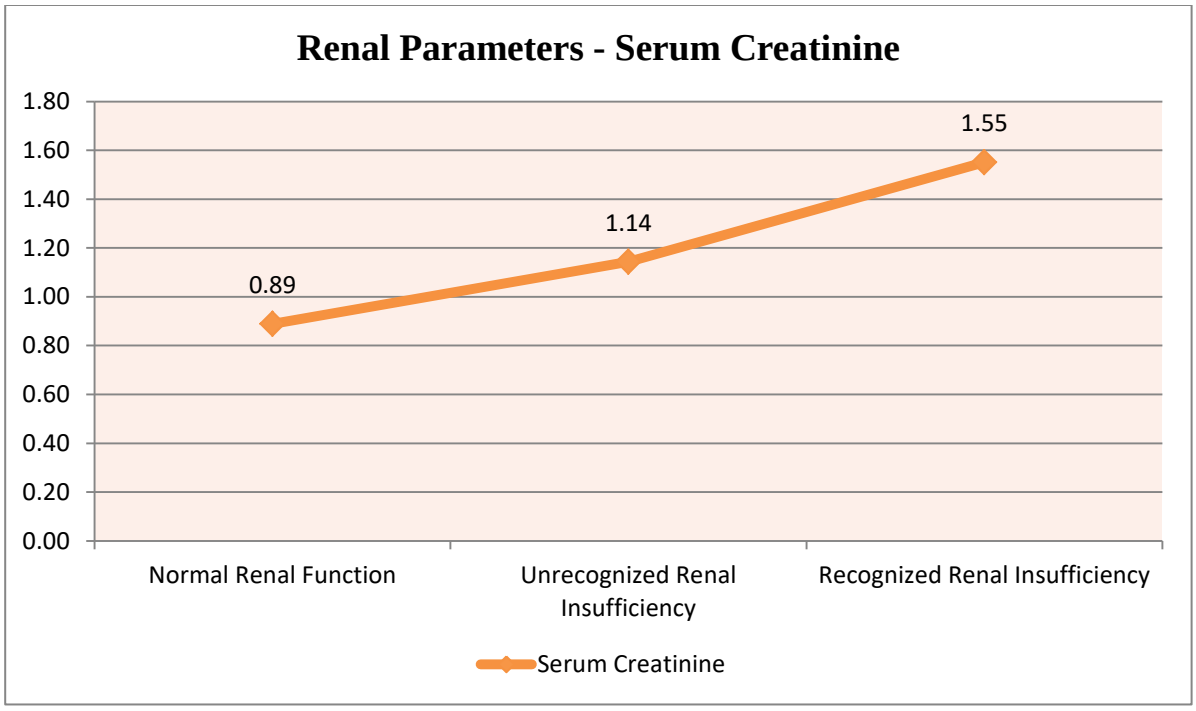
When the alcohol intake status between three groups was analysed statistically using fishers exact test, the difference in percentage of alcoholic subjects in normal renal function group (52.33%), unrecognized renal insufficiency group (0.00%) and recognized renal insufficiency group (51.61%) was found to be statistically insignificant (p >0.05).

Conclusion

We can conclude that the variable alcohol intake is normally distributed across the three study groups and has no bearing on renal function among stroke patients.

Renal Parameters





Renal Parameters		Blood Urea	Serum Creatinine
Normal Renal Function	Mean	26.19	0.89
	SD	8.58	0.17
Unrecognized Renal Insufficiency	Mean	32.29	1.14
	SD	6.97	0.10
Recognized Renal Insufficiency	Mean	40.19	1.55
	SD	19.57	0.28
P value Single Factor ANOVA Test		<0.0001	<0.0001

Results

While analyzing renal parameters in relation to renal function among stroke patients, the observed mean blood urea levels were 26.19 in normal renal function group, 32.29 in unrecognized renal insufficiency group and 40.19 in recognized renal insufficiency group. Similarly the observed mean serum

creatinine levels were 0.89 in normal renal function group, 1.14 in unrecognized renal insufficiency group and 1.55 in recognized renal insufficiency group

Discussion

When the renal parameters distribution between three groups was analysed statistically using single factor ANOVA test, the mean difference of blood urea values in unrecognized renal function group compared to normal renal function group was 6.09 (19 % increase) and between recognized renal insufficiency group compared to unrecognized renal insufficiency group was 7.91 (20 % increase). This was found to be statistically significant ($p < 0.05$). Similarly the mean difference of serum creatinine values in unrecognized renal function group compared to normal renal function group was 0.25 (22% increase) and between recognized renal insufficiency group compared to unrecognized renal insufficiency group was 0.41 (26 % increase). This was found to be statistically significant ($p < 0.05$).

It is evident that there is a statistically significant progressive increase in renal parameters across the three groups. On calculating the effect size of blood urea using Cohen's "d" value ($d = 1.19$), a high practical significance was observed (88% of study subjects with blood urea levels over 40 will have recognized renal

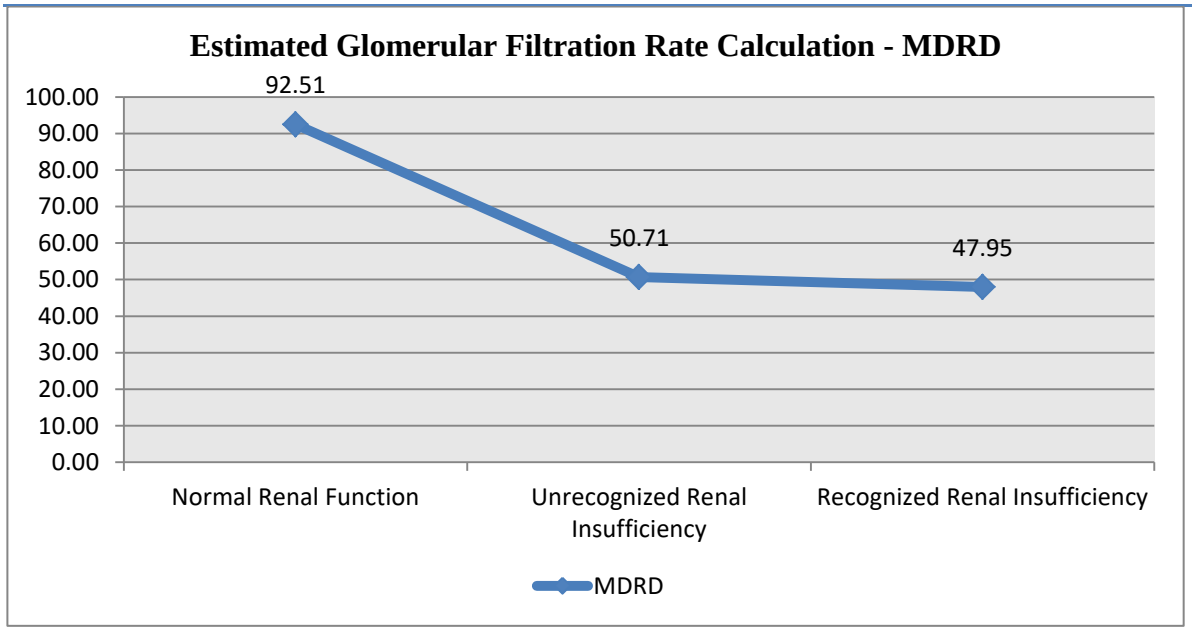
insufficiency and 69% of study subjects with blood urea levels between 32-40 will have unrecognized renal insufficiency).

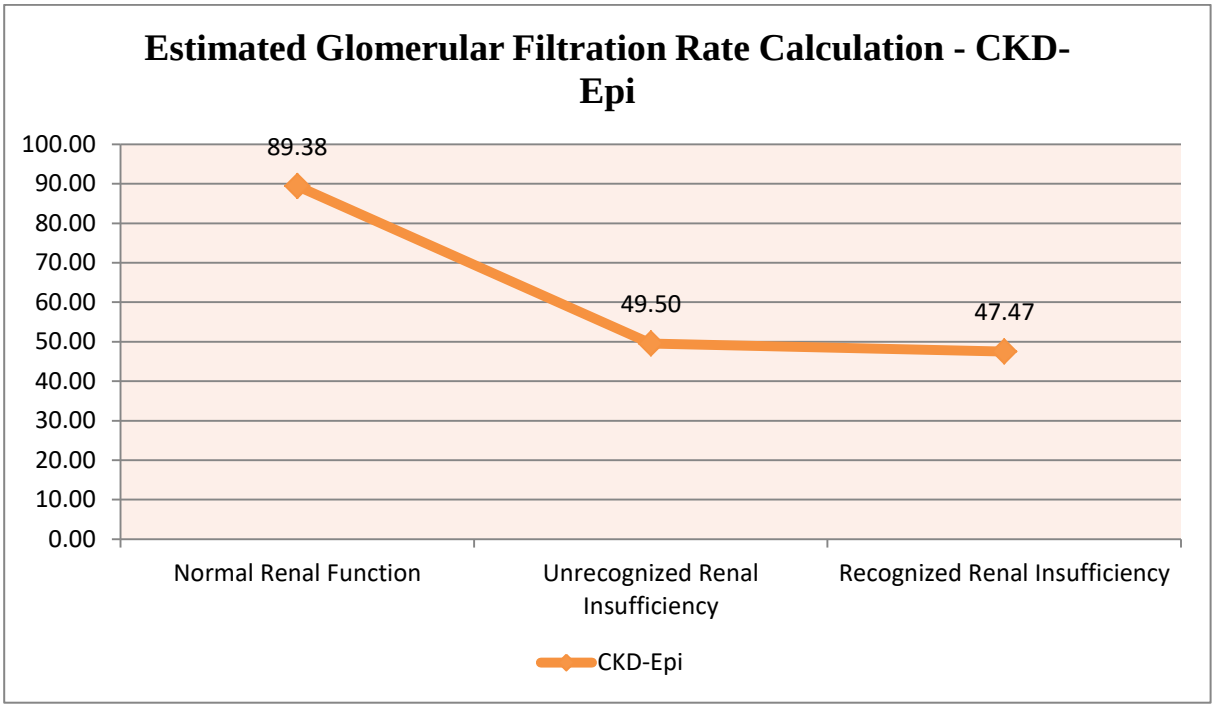
Similarly on calculating the effect size of serum creatinine using Cohen's "d" value (d = 3.00), a high practical significance was observed (100% of study subjects with serum creatinine levels over 1.55 will have recognized renal insufficiency and 90% of study subjects with serum creatinine between 1.14-1.55 will have unrecognized renal insufficiency) .

Conclusion

We can conclude that blood urea and serum creatinine levels are low in patients with normal renal function compared with unrecognized renal insufficiency and recognized renal insufficiency.

EFGR





Estimated Glomerular Filtration Rate Calculation		MDRD	CKD-Epi
Normal Renal Function	Mean	92.51	89.38
	SD	19.58	14.32
Unrecognized Renal Insufficiency	Mean	50.71	49.50
	SD	4.07	3.28
Recognized Renal Insufficiency	Mean	47.95	47.47
	SD	10.65	10.87
P value Single Factor ANOVA Test		<0.0001	<0.0001

Results

While analyzing eGFR parameters in relation to renal function among stroke patients, the observed mean MDRD levels were 92.51 in normal renal function group, 50.71 in unrecognized renal insufficiency group and 47.95 in recognized

renal insufficiency group. Similarly the observed mean CKD-EPI levels were 89.38 in normal renal function group, 49.50 in unrecognized renal insufficiency group and 47.47 in recognized renal insufficiency group

Discussion

When the eGFR parameters distribution between three groups was analysed statistically using single factor ANOVA test, the mean difference of MDRD values in unrecognized renal function group compared to normal renal function group was 41.80 (82 % decrease) and between recognized renal insufficiency group compared to unrecognized renal insufficiency group was 2.77 (6 % decrease). This was found to be statistically significant ($p < 0.05$).

Similarly the mean difference of CKD-EPI values in unrecognized renal function group compared to normal renal function group was 59.88 (81% decrease) and between recognized renal insufficiency group compared to unrecognized renal insufficiency group was 2.03 (4 % decrease). This was found to be statistically significant ($p < 0.05$).

It is evident that there is a statistically significant progressive increase in eGFR parameters across the three groups. On calculating the effect size of MDRD using Cohen's "d" value ($d = 3.00$), a high practical significance was observed (100% of study subjects with MDRD levels under 47.95 will have recognized

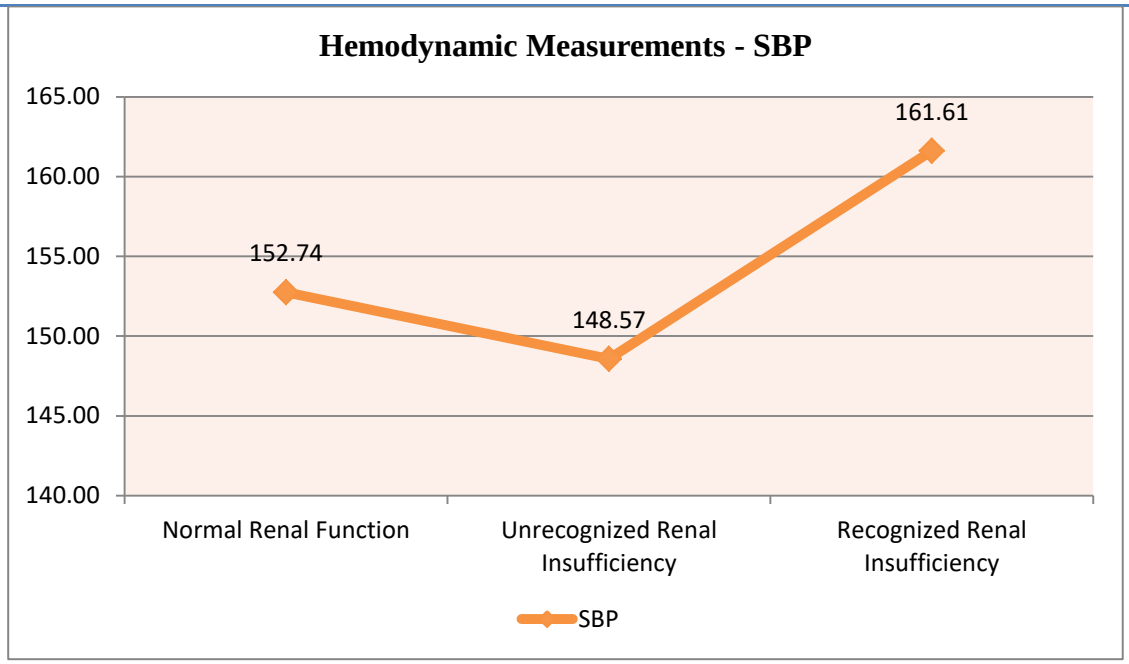
renal insufficiency and 81% of study subjects with MDRD levels between 51-48 will have unrecognized renal insufficiency) .

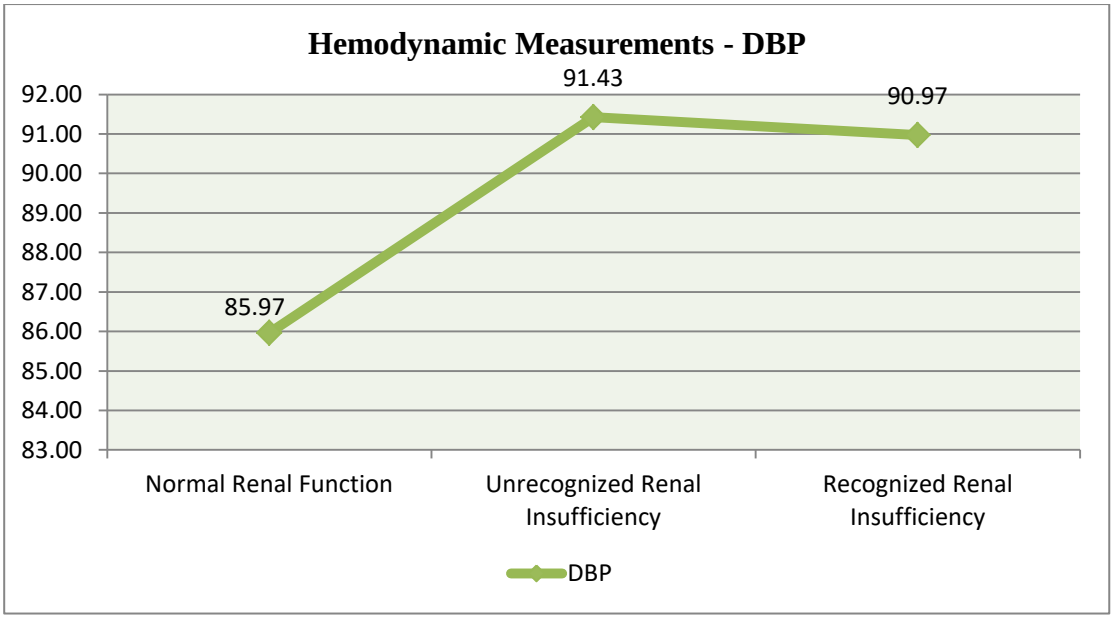
Similarly on calculating the effect size of CKD-EPI using Cohen's "d" value (d = 3.00), a high practical significance was observed (100% of study subjects with CKD-EPI levels under 47.47 will have recognized renal insufficiency and 86% of study subjects with CKD-EPI between 50-47 will have unrecognized renal insufficiency).

Conclusion

We can conclude that MDRD and CKD-EPI levels were significantly lower in patients with recognized renal insufficiency compared with unrecognized renal insufficiency.

Hemodynamic Measurements





Hemodynamic Measurements		SBP	DBP
Normal Renal Function	Mean	152.74	85.97
	SD	27.29	11.66
Unrecognized Renal Insufficiency	Mean	148.57	91.43
	SD	18.64	10.69
Recognized Renal Insufficiency	Mean	161.61	90.97
	SD	23.39	14.46
P value Single Factor ANOVA Test		<0.0001	<0.0001

Results

While analyzing hemodynamic parameters in relation to renal function among stroke patients, the observed mean SBP was 152.74 in normal renal function group, 148.57 in unrecognized renal insufficiency group and 161.67 in recognized renal insufficiency group and observed DBP was 85.97 in normal renal function group, 91.43 in unrecognized renal insufficiency group and 90.97 in recognized renal insufficiency group.

Discussion

When the hemodynamic parameters distribution between three groups was analysed statistically using single factor ANOVA test, the mean difference of SBP values in unrecognized renal function group compared to normal renal function group was 4.17 (3% decrease) and between recognized renal insufficiency group compared to unrecognized renal insufficiency group was 13.04 (8 % increase). This was found to be statistically significant ($p < 0.05$).

Similarly the mean difference of DBP values in unrecognized renal function group compared to normal renal function group was 5.46 (5% increase) and between recognized renal insufficiency group compared to unrecognized renal insufficiency group was 0.46 (1 % decrease). This was found to be statistically significant ($p < 0.05$).

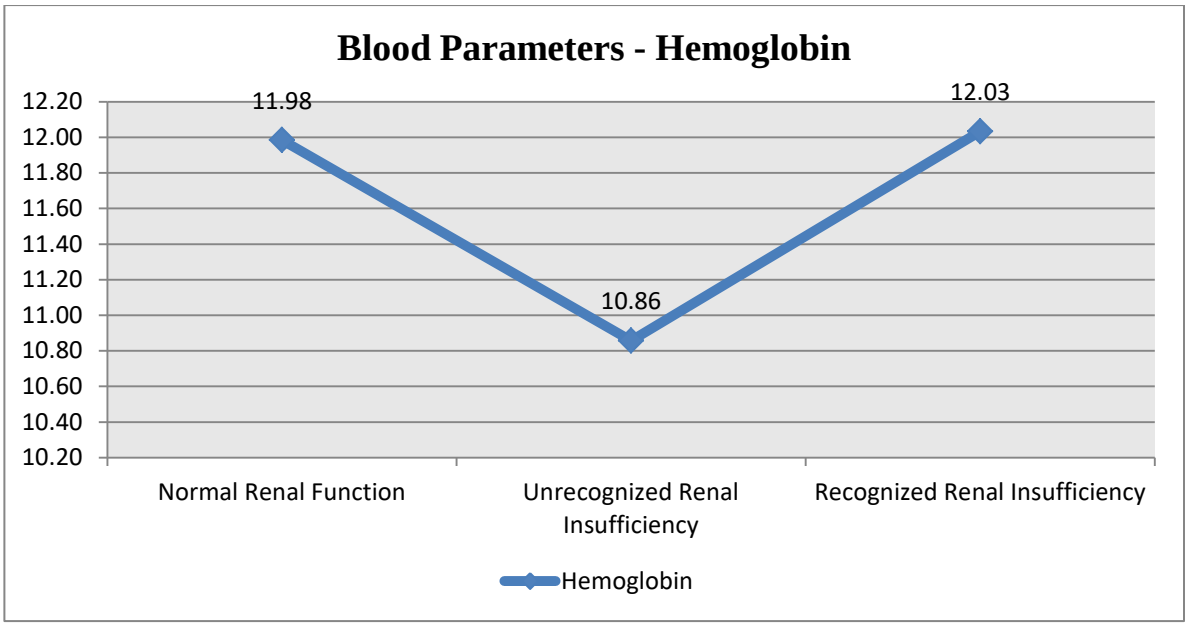
On calculating the effect size of SBP using Cohen's "d" value ($d = 0.38$), a low practical significance was observed (65% of study subjects with SBP levels above 162 will have recognized renal insufficiency and 53% of study subjects with SBP between 149-162 will have unrecognized renal insufficiency) .

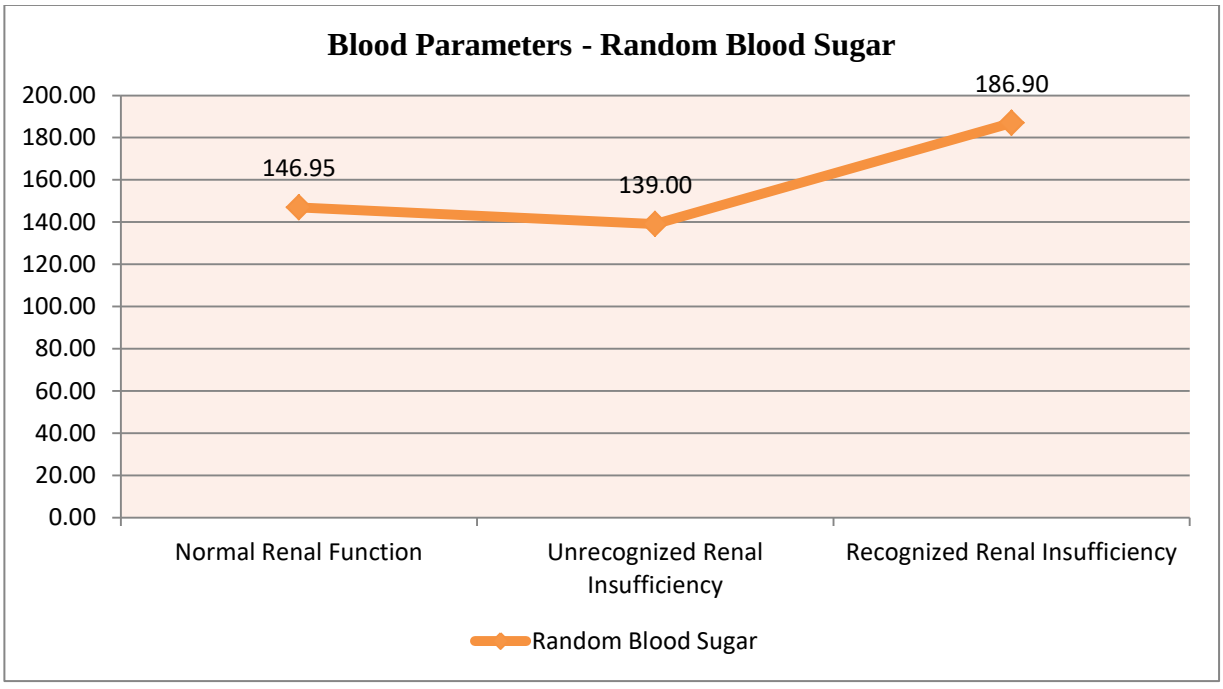
Similarly on calculating the effect size of DBP using Cohen's "d" value ($d = 0.41$), a low practical significance was observed (65% of study subjects with DBP levels above 91 will have recognized and unrecognized renal insufficiency).

Conclusion

We can conclude that both systolic and diastolic blood pressure level is significantly higher in patients with recognized renal insufficiency compared with unrecognized renal insufficiency.

Blood Parameters





Blood Parameters		Haemoglobin	Random Blood Sugar
Normal Renal Function	Mean	11.98	146.95
	SD	1.76	97.97
Unrecognized Renal Insufficiency	Mean	10.86	139.00
	SD	1.46	80.38
Recognized Renal Insufficiency	Mean	12.03	186.90
	SD	2.27	98.17
P value Single Factor ANOVA Test		0.3171	0.1539

Results

While analyzing blood parameters in relation to renal function among stroke patients, the observed mean Hb level was 11.98 in normal renal function group, 10.86 in unrecognized renal insufficiency group and 12.03 in recognized renal insufficiency group. Similarly the observed mean RBS was 146.95 in normal renal function group, 139.00 in unrecognized renal insufficiency group and 196.90 in recognized renal insufficiency group.

Discussion

When the blood parameters distribution between three groups was analysed statistically using single factor ANOVA test, the mean difference of Hb in unrecognized renal function group compared to normal renal function group was 1.13 (10 % decrease) and between recognized renal insufficiency group compared to unrecognized renal insufficiency group was 1.18 (10 % increase). This was found to be statistically significant ($p < 0.05$).

Similarly the mean difference of RBS values in unrecognized renal function group compared to normal renal function group was 7.95 (6% decrease) and between recognized renal insufficiency group compared to unrecognized renal insufficiency group was 47.90 (74% increase). This was found to be statistically significant ($p < 0.05$).

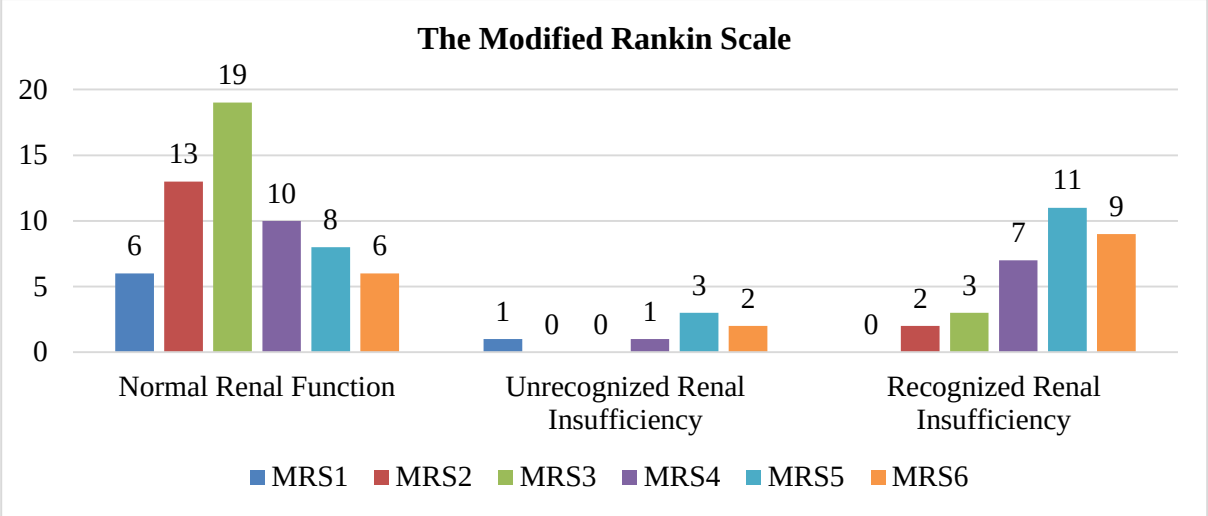
It is evident that there is a statistically significant progressive decrease and increase in blood parameters across the three groups. On calculating the effect size of Hb using Cohen's "d" value ($d = 0.03$), a very low practical significance was observed (54% of study subjects with Hb levels over 12.03 will have recognized and unrecognized renal insufficiency).

Similarly on calculating the effect size of RBS using Cohen's "d" value ($d = 0.43$), a low practical significance was observed (65% of study subjects with RBS levels above 186 will have recognized renal insufficiency).

Conclusion

We can conclude that Haemoglobin and RBS levels were significantly higher in patients with recognized renal insufficiency compared with unrecognized renal insufficiency.

Modified Rankin Scale



The Modified Rankin Scale	Normal Renal Function	%	Unrecognized Renal Insufficiency	%	Recognized Renal Insufficiency	%
MRS 1	6	9.68	1	14.29	0	0.00
MRS 2	13	20.97	0	0.00	2	6.45
MRS 3	19	30.65	0	0.00	3	9.68
MRS 4	10	16.13	1	14.29	7	22.58
MRS 5	8	12.90	3	57.14	11	35.48
MRS 6	6	9.67	2	28.57	9	29.0
Total	62	100.00	7	100.00	31	100.00

The Modified Rankin Scale Distribution	Normal Renal Function	Unrecognized Renal Insufficiency	Recognized Renal Insufficiency
Mean	3.32	4.43	4.65
SD	1.47	1.62	1.17
P value Single Factor ANOVA Test			0.0001

Results

While analyzing MRS distribution in relation to renal function among stroke patients, it was observed that majority of the study subjects in normal renal function group were distributed in MRS 3 group (n=19, 30.65%), MRS 5 group in unrecognized renal insufficiency group (n=4, 57.14%) and MRS 5 group in recognized renal insufficiency group (n=11, 35.48%).

Discussion

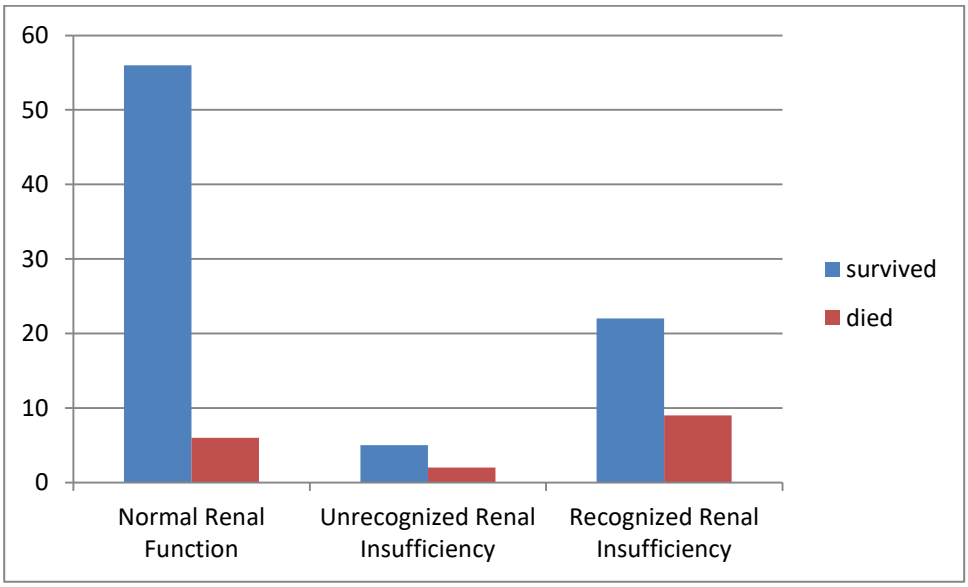
When the MRS distribution between three groups was analysed statistically using single factor ANOVA test, the mean difference of MRS in unrecognized renal function group compared to normal renal function group was 1.11 (25 % increase) and between recognized renal insufficiency group compared to unrecognized renal insufficiency group was 0.22 (5 % increase). This was found to be statistically significant ($p < 0.05$). Similarly on calculating the effect size of MRS using Cohen's "d" value ($d = 1.00$), a high practical significance

was observed (84% of study subjects with MRS above 5 will have recognized and unrecognized renal insufficiency).

Conclusion

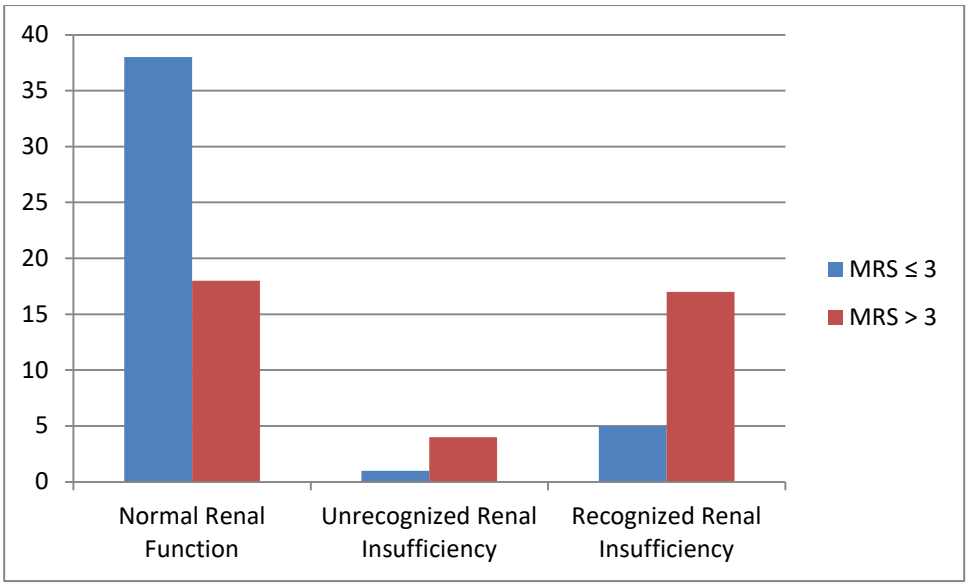
We can conclude that MRS was significantly higher in patients with recognized renal insufficiency compared to unrecognized renal insufficiency patients.

Mortality Rate



	Normal Renal Function	%	Unrecognized Renal Insufficiency	%	Recognized Renal Insufficiency	%
Survived	56	90.32	5	71.42	22	70.96
Deaths	6	9.67	2	28.57	9	29.03
Total	62	100	7	100	31	100
					0.04053	

Severity disability rate



	Normal Renal Function	%	Unrecognized Renal Insufficiency	%	Recognized Renal Insufficiency	%
MRS ≤ 3	38	67.85	1	20	5	22.72
MRS > 3	18	32.14	4	80	17	72.27
Total	56	100	5	100	22	100
					0.0001	

Discussion

Of the 100 patients with stroke included in the study, 62% had normal renal function, 31% had recognized renal insufficiency, and 7% had unrecognized renal insufficiency. Mortality rates are higher in patients with recognized and unrecognized renal insufficiency compared with patients with normal renal function (29%, %, and 28.5% and 9.6%) respectively, $P < 0.05$). Similarly, severe disability rates at discharge are also higher in patients with recognized

and unrecognized renal insufficiency compared with patients with normal renal function (72.27%, 80 %, and 32.14%) respectively, $P < 0.05$.

Data Analysis

Descriptive statistics were done for all data and were reported in terms of mean values and percentages. Suitable statistical tests of comparison were done. Continuous variables were analyzed with the unpaired t test and ANOVA.. Categorical variables were analyzed with the Chi-Square Test and Fisher Exact Test. Statistical significance was taken as $P < 0.05$. The data was analysed using SPSS version 16 and Microsoft Excel 2007.

CONCLUSION

1. Unrecognized renal insufficiency is found to be a common comorbidity among patients with acute stroke in our study.

2. Unrecognized renal insufficiency is significantly common among older age group and more frequently in females compared to male in our study group.

3. Mortality rate and severe disability rate are higher in patients with recognized and unrecognized renal insufficiency compared to patients with normal renal function.

4. Our study did not show any significant difference in all outcomes between recognized and unrecognized renal insufficiency.

Limitations of the Study

1. Evaluation of renal function was based on a single serum creatinine measurement taken on admission. Single admission creatinine levels may not reflect their baseline renal function.

2. Less number of patient are included in study.

3. The current study demonstrated only unrecognized renal insufficiency in acute stroke is associated with adverse short-term outcomes. However, long term outcome of stroke patients with renal dysfunction were not measured.

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PROFORMA

NAME: AGE: SEX:

ADDRESS: CONTACT NO:

COMPLAINTS:

HISTORY

ALCOHOLISM YES NO DURATION:

HEAD INJURY YES NO

HYPOTHYROIDISM YES NO

KIDNEY DISEASE YES NO

SMOKER YES NO

H/O MEDICATION -

RELEVANT CLINICAL EXAMINATION:

GENERAL EXAMINATION

SYSTEMIC EXAMINATION:

CARDIOVASCULAR:

RESPIRATORY:

ABDOMEN :

CNS:

LABORATORY INVESTIGATIONS

HB: TC: PLATELET:

RBS RFT:

Lipid Profile

Urine Routine

CT/MRI Brain:

COMMENT:

CONSENT FORM

GOVT. STANLEY MEDICAL COLLEGE, CHENNAI – 600001
INFORMED CONSENT

Study of Clinical Significance of Unrecognized Renal Dysfunction in Patients with Acute Stroke

Place of study: Government Stanley Medical College, Chennai

I ……. have been informed about the details of the study in my own language.

I have completely understood the details of the study.

I am aware of the possible risks and benefits, while taking part in the study.

I agree to collect samples of blood/saliva/urine/tissue if study needs.

I understand that I can withdraw from the study at any point of time and even then, I can receive the medical treatment as usual.

I understand that I will not get any money for taking part in the study.

I will not object if the results of this study are getting published in any medical journal, provided my personal identity is not revealed.

I know what I am supposed to do by taking part in this study and I assure that I would extend my full cooperation for this study.

Volunteer:	Witness:
Name and address	Name and address
Signature/thumb impression:	Signature/thumb impression
Date:	Date:

Investigator Signature and date

GOVT. STANLEY MEDICAL COLLEGE, CHENNAI – 600001

INFORMED CONSENT

Study of Clinical Significance of Unrecognized Renal Dysfunction in Patients with Acute Stroke

AT GOVERNMENT STANLEY HOSPITAL, CHENNAI.

நான் இந்த ஆராய்ச்சியில் விவரங்களை முற்றிலும் புரிந்து கொண்டேன்.

ஆய்வில் பங்கு எடுத்து போது, சாத்தியமான அபாயங்கள் மற்றும் பயன்களை பற்றி நான் அறிந்துள்ளேன்.

நான் எந்தவொரு வேளையிலும் ஆய்வில் இருந்து திரும்ப முடியும், அதன் பின்னர், நான் வழக்கம் போல் மருத்துவ சிகிச்சை பெற முடியும் என்று புரிந்துகொள்கிறேன்

நான் ஆய்வில் பங்கு எடுத்து பணம் எதையும் பெற முடியாது என்று அறிந்துள்ளேன்.

இந்த ஆய்வின் முடிவுகள் எந்த மெடிக்கல் ஜர்னலில் வெளியிடப்பட இருந்தால் நான் எதிர்க்கவில்லை, என் தனிப்பட்ட அடையாளத்தை வெளிப்படுத்தப்பட்டு இருக்க கூடாது.

நான் இந்த ஆய்வில் பங்கெடுப்பதன் மூலம் நான் என்ன செய்ய போகிறேன் என்று தெரியும்

நான் இந்த ஆய்வில் என் முழு ஒத்துழைப்பையும் கொடுப்பேன் என்று உறுதியளிக்கிறேன்.

தன்னார்வளர்	சாட்சி
பெயர் மற்றும் முகவரி	பெயர் மற்றும் முகவரி
கையொப்பம் / விரல் ரேகை:	கையொப்பம் / விரல் ரேகை:
ஆராய்ச்சியாளராக	கையொப்பம் மற்றும் தேதி

ETHICAL COMMITTEE LETTER

INSTITUTIONAL ETHICAL COMMITTEE,
STANLEY MEDICAL COLLEGE, CHENNAI-1

Title of the Work : A study of clinical significance of unrecognized renal dysfunction in patients with stroke

Principal Investigator : Dr P Kalavathi

Designation : PG MD (General Medicine)

Department : Department of General Medicine
Government Stanley Medical College,
Chennai-01

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 24.02.2017 at the Council Hall, Stanley Medical College, Chennai-1 at 2PM

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

MEMBER SECRETARY, 6/2/17.
IEC, SMC, CHENNAI
MEMBER SECRETARY
ETHICAL COMMITTEE,
STANLEY MEDICAL COLLEGE
CHENNAI-600 001.

APPENDIX

S.No	Age	Sex	Infarct	Hemo rrhage	SHT	DM	CAD	Smoker	Alcoholic	Cr	MDRD	CKD-EPI	MRS	SBP	DBP	Hb	RBS	Dys-lipidemia
1	56	M	yes	-	yes	-	-	yes	-	1.4	55.7	55.8	3	190	100	11	96	yes
2	40	M	yes	-	-	yes	-	yes	yes	1.4	59.7	62.4	5	140	90	12	136	yes
3	36	M	-	yes	yes	-	-	yes	yes	1.4	60.95	64.2	5	200	100	16	130	yes
4	49	M	yes	-	-	-	-	-	yes	1.2	68.4	70.6	2	160	80	14	89	
5	55	M	yes	-	-	-	-	yes	yes	0.7	124.4	106.2	3	130	80	14	61	yes
6	43	M	-	yes	yes	yes	-	-	yes	1.5	54	56.2	5	180	90	12	193	
7	48	M	yes	-	-	-	-	yes	yes	1.2	69	71	2	120	80	13	74	
8	40	M	-	yes	-	-	-	yes	yes	0.9	99	106.5	6	220	110	14	95	
9	75	M	yes	-	-	-	-	-	-	1	77	73.3	1	150	80	9	109	
10	55	M	-	yes	-	-	-	yes	yes	0.9	93	95.8	3	160	100	10	101	yes
11	64	F	-	yes	yes	-	-	-	-	1.2	48	47.7	6	180	110	12	114	yes
12	62	M	-	yes	yes	yes	-	yes	yes	1.6	46	45.5	5	190	100	16	264	yes
13	58	F	yes	-	yes	-	-	-	-	1.2	49	49.8	6	140	90	10	156	yes
14	50	M	yes	-	yes	-	-	yes	yes	1	84	87.4	2	130	70	11	124	
15	40	M	yes	-	yes	-	-	-	-	0.8	114	111.7	1	140	80	13	166	
16	63	M	yes	-	yes	yes	-		yes	1.2	65	64	3	160	90	12	68	
17	64	M	yes	-	yes	-	-	-	-	0.6	144	106.3	3	150	80	9	108	
18	60	M	yes	-	yes	-	-	yes	yes	0.8	105	97	3	160	90	8	96	yes
19	58	M	yes	-	-	yes	-	yes	yes	1.5	51	50.6	2	160	80	14	308	yes
20	45	M	yes	-	yes	-	-	-	yes	0.8	111	107	3	140	80	11	82	
21	65	M	yes	-	yes	-	-	-	yes	0.9	90	89	4	160	100	12	118	
22	45	M	yes	-	yes	-	-	-	yes	0.9	97	103	2	130	90	14	85	
23	70	M	yes	-	-	-	-	-	-	1.2	63	61	5	150	80	10	112	
24	68	M	-	yes	yes	-	-	-	yes	1.6	46	44	4	190	110	11	95	yes
25	65	M	yes	-	yes	-	-	yes	yes	0.8	103	93	4	150	80	13	100	yes
26	58	F	yes	-	yes	yes	-	-	-	1.7	33	33	6	160	90	9	264	yes
27	64	F	yes	-	-	-	-	-	-	0.9	67	68	4	150	90	11	142	
28	55	M	-	yes	yes	-	-	-	yes	1.4	56	56	6	180	120	13	123	yes

S.No	Age	Sex	Infarct	Hemo rrhage	SHT	DM	CAD	Smoker	Alcoholic	Cr	MDRD	CKD-EPI	MRS	SBP	DBP	Hb	RBS	Dys-lipidemia
29	64	M	yes	-	-	-	-	yes	yes	1.2	65	64	3	140	80	10	84	yes
30	68	M	yes	-	-	yes	-	-	-	1.4	54	51	6	130	80	10	386	
31	40	M	-	yes	yes	-	-	yes	yes	1.2	71	75	5	140	100	15	280	
32	52	M	yes	-	-	-	-	yes	yes	0.9	94	98	1	160	80	12	90	yes
33	60	M	yes	-	yes	yes	-	yes	yes	1.3	60	59	3	140	70	12	186	yes
34	61	M	yes	-	SHT	-	-	yes	yes	0.8	105	96	3	130	80	10	104	yes
35	50	F	yes	-	_	-	-	yes	yes	1.6	36	37	6	160	80	12	84	yes
36	75	F	yes	-	yes	-	-	-	-	0.7	86	85	5	140	70	9	366	yes
37	64	F	-	yes	_	-	-	_	-	0.6	107	96	5	170	120	11	140	yes
38	72	F	yes	-	yes	yes	-	_	-	1.5	36	35	6	130	80	8	232	yes
39	62	M	-	yes	yes	-	-	_	-	0.8	104	96	3	180	90	16	78	
40	70	M	yes	-	yes	-	-	yes	yes	0.8	102	91	5	140	80	11	160	
41	45	M	yes	-	yes	yes	yes	yes	yes	1.2	70	73	1	120	70	12	183	
42	62	F	yes	-	-	-	-	_	-	0.9	91	91	3	160	90	13	106	
43	56	M	-	yes	yes	yes	-	_	-	1.7	45	44	5	150	100	12	290	yes
44	57	M	yes	-	yes	yes	-	yes	yes	1	82	83	2	140	90	14	242	yes
45	64	M	-	yes	yes	yes	-	yes	yes	1.3	59	58	5	170	80	10	196	
46	66	F	yes	-	yes	-	-	-	-	1.7	32	31	5	160	70	10	90	
47	54	F	yes	-	yes	yes	-	-	-	0.8	79	84	1	180	90	11	214	yes
48	69	M	yes	-	yes	yes	-	yes	-	1.3	58	56	2	150	90	12	184	yes
49	62	M	-	yes	yes	yes	-	yes	yes	2.2	32	31	6	200	110	12	440	yes
50	58	F	yes	-	yes	-	-	-	-	1.2	49	50	1	130	80	12	88	
51	52	M	-	yes	yes	-	-	yes	yes	0.9	94	98	4	160	80	14	121	
52	46	M	-	yes	yes	-	-	yes	yes	1.2	69	72	3	220	100	13	86	
53	72	M	yes	-	-	-	-	-	-	1.2	63	60	3	170	90	10	77	
54	58	M	yes	-	yes	yes	-	-	-	0.8	106	99	4	130	70	12	344	
55	64	M	yes	-	yes	-	yes	-	-	0.8	103	94	3	120	80	9	95	
56	54	F	yes	-	yes	-	-	-	-	0.9	94	97	2	150	80	12	112	

S.No	Age	Sex	Infarct	Hemo rrhage	SHT	DM	CAD	Smoker	Alcoholic	Cr	MDRD	CKD-EPI	MRS	SBP	DBP	Hb	RBS	Dys-lipidemia
57	50	M	-	yes	yes	-	-	yes	yes	1.1	75	78	6	180	80	10	168	yes
58	68	F	yes	-	-	yes	-	-	-	1.2	48	47	4	130	90	12	304	yes
59	56	M	yes	-	yes		-	yes	-	1.4	56	56	3	140	90	11	102	
60	62	M	yes	-	yes	yes	-	alcohol, smoker	-	0.8	104	96	2	120	80	12	192	
61	40	F	yes	-	-	-	-	yes	yes	0.8	84	92	6	90	60	14	84	
62	58	M	-	yes	yes	yes	yes	yes	yes	1.4	55	55	6	140	90	16	210	yes
63	68	M	yes	-	yes	-	-	yes	-	1.3	58	56	5	160	90	12	132	
64	72	F	yes	-	-	-	-	-	-	1	58	56	5	160	90	9	80	yes
65	54	F	yes	-	-	-	-	-	-	0.7	93	98	1	130	80	11	144	yes
66	48	M	-	yes	yes	-	-	yes	yes	2.4	31	31	6	190	100	14	128	yes
67	56	M	yes	-	yes	-	-	yes	-	0.6	148	112	2	140	90	13	90	
68	61	M	yes	-	-	-	-	yes	-	0.8	104	96	2	150	80	12	86	
69	57	M	yes	-	yes	yes	-	yes	yes	0.7	124	105	3	130	80	14	284	yes
70	48	M	-	yes	yes	-	-	yes	yes	0.8	110	106	5	130	90	11	100	yes
71	64	M	yes	-	yes	-	yes	yes	yes	1.2	65	64	4	140	80	14	130	yes
72	54	M	yes	-	yes	yes	-		yes	0.8	107	101	2	120	70	12	242	
73	52	M	yes	-	yes	-	-	yes	yes	0.9	94	98	2	180	80	12	94	yes
74	69	M	yes	-	yes	-	-	-	-	1.3	58	56	4	170	90	12	85	
75	46	M	-	yes	yes	-	-	yes	yes	0.7	129	113	6	160	100	13	114	
76	74	M	yes	-	-	-	-	yes	-	1.3	57	54	6	160	80	11	82	yes
77	54	M	-	yes	yes	-	-	-	yes	1.8	42	42	4	170	110	12	68	
78	55	M	yes	-	-	yes	-	-	-	0.8	107	101	3	140	80	13	224	yes
79	62	M	yes	-	yes	yes	-	-	yes	1.5	50	49	4	100	70	14	277	yes
80	90	F	yes	-	yes	-	-	-	-	1	55	50	5	140	80	9	74	
81	60	F	yes	-	yes	-	-	-	-	0.8	78	80	4	130	90	11	152	
82	48	F	yes	-	-	-	-	-	-	0.9	71	76	3	100	70	12	83	
83	70	F	yes	-	yes	yes	-	-	-	0.7	88	88	4	180	90	10	540	yes
84	64	F	yes	-	yes	yes	-	-	-	2.2	24	23	5	160	90	13	323	yes
85	67	M	-	-	yes	-	-	-	-	1.2	64	62	5	160	90	13	127	yes
86	66	F	yes	-	yes	yes	-	-	-	0.8	76	77	6	200	100	11	366	yes
87	62	F	yes	-	yes	yes	-	-	-	1.4	41	40	4	140	60	8	144	

S.No	Age	Sex	Infarct	Hemo rrhage	SHT	DM	CAD	Smoker	Alcoholic	Cr	MDRD	CKD-EPI	MRS	SBP	DBP	Hb	RBS	Dys-lipidemia
88	58	F	yes	-	yes	yes	-	-	-	0.8	78	81	4	200	110	9	480	yes
90	65	M	yes	-	-	-	-	yes	-	0.9	90	89	3	160	90	12	93	
91	52	M	yes	-	yes	-	-	yes	yes	0.8	108	102	2	180	80	15	103	
92	50	M	-	yes	yes	-	yes	-	yes	0.9	95	99	3	210	120	14	93	
93	58	M	yes	-	-	yes	-	-	-	1.8	41	41	4	160	90	14	293	yes
94	60	M	yes	-	yes	-	-	yes	yes	0.8	105	97	4	200	90	13	88	yes
95	68	F	yes	-	-	-	-	-	-	1.2	48	46	5	160	100	12	157	yes
96	62	M	yes	-	yes	-	-	yes	-	0.8	104	96	6	190	100	14	86	
97	54	M	yes	-	-	-	-	yes	-	0.8	107	101	3	130	80	13	112	yes
98	70	F	yes	-	yes	yes	yes	-	-	1.3	43	42	5	150	100	8	90	
99	58	F	yes	-	yes	-	yes	-	-	0.7	91	96	2	140	90	12	137	
100	42	M	-	yes	-	-	-	-	yes	1.5	56	57	5	190	120	16	163	

ABBREVIATIONS

ACE- Angiotensin converting enzyme

ACTH - Adrenocorticotropic hormone

ADH - *Antidiuretic hormone*

AHA – American Heart Association

AKI – Acute kidney injury

ARF – Acute renal failure

ATN – Acute tubular necrosis

AV – Arterio venous

BP – Blood pressure

CAD – Coronary artery disease

CKD – Chronic kidney disease

Cr – Creatinine

CKD – EPI - *Chronic Kidney Disease* Epidemiology Collaboration

CVA – Cerebrovascular accident

DM – Diabetes mellitus

ECG – Electrocardiogram

EGFR – Estimated glomerular filtration rate

ERPF – Effective renal plasma flow

HIV – *Human immunodeficiency virus*

KIM – Kidney injury molecule

MCA – Middle cerebral artery

MDRD - Modification of Diet in Renal Disease

MRS – Modified rankin scale

NGAL - Neutrophil gelatinase-associated lipocalin

RBF – Renal blood flow

RPF – Renal plasma flow

SAH – Subarachnoid hemorrhage

SHT – Systemic hypertension

TIA – Transient ischemic attack

UTI – Urinary tract infection